Is (poly-) substance use associated with impaired inhibitory control? A mega-analysis controlling for confounders

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Is (poly-) substance use associated with impaired inhibitory control?

A mega-analysis controlling for confounders

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Highlights:

- The association between polysubstance use and inhibition is as-yet-unknown
- This association was tested with a mega-analysis using individual participant data
- Only lifetime cannabis use was associated with suboptimal inhibition (stop-task)
- Lifetime cannabis use moderated tobacco's effect on response inhibition
- In cannabis non-users only, tobacco use was associated with suboptimal inhibition

Abstract

Many studies have reported that heavy substance use is associated with impaired response inhibition. Studies typically focused on associations with a single substance, while polysubstance use is common. Further, most studies compared heavy users with light/non-users, though substance use occurs along a continuum. The current mega-analysis accounted for these issues by aggregating individual data from 43 studies (3610 adult participants) that used the Go/No-Go (GNG) or Stop-signal task (SST) to assess inhibition among mostly "recreational" substance users (i.e., the rate of substance use disorders was low). Main and interaction effects of substance use, demographics, and task-characteristics were entered in a linear mixed model. Contrary to many studies and reviews in the field, we found that only lifetime cannabis use was associated with impaired response inhibition in the SST. An interaction effect was also observed: the relationship between tobacco use and response inhibition (in the SST) differed between cannabis users and non-users, with a negative association between tobacco use and inhibition in the cannabis non-users. In addition, participants' age, education level, and some task characteristics influenced inhibition outcomes. Overall, we found limited support for impaired inhibition among substance users when controlling for demographics and task-characteristics.

Keywords:

Polysubstance use; Response inhibition; Stop-signal task; Go/No-Go task; Mega-analysis.

Introduction

1.1. Substance Use and Response Inhibition

1.1.1. What is response inhibition and how does it relate to substance use?

Inhibitory control, also known as response inhibition, has been defined as the ability to control one's attention, behavior, thoughts, and/or emotions to override a strong internal predisposition or external lure, and instead do what is more appropriate or needed (Diamond, 2013). Loss of control over one's behavior is a defining characteristic of addiction. The DSM-5 lists characteristics such as 'taking larger amounts or over a longer period than was intended' and 'unsuccessful efforts to cut down or control alcohol use' to define the loss of control over drinking (American Psychiatric Association, 2013). Moreover, inhibitory control has been proposed to play an important role at different stages of the addiction cycle, i.e., 1) initial use of substance; 2) transition from recreational use to heavier use and abuse; 3) continuation of use for those who get addicted; 4) relapse after abstinence (e.g., Garavan, Potter, Brennan, & Foxe, 2015; Koob & Volkow, 2010). Furthermore, the dual process model on addiction proposes that an imbalance between a hyper-sensitized impulsive system, which is responsible for cue-reactivity, and a compromised reflective or control system (including inhibition of impulses) are important in the development of addiction (Bechara, 2005; Gladwin, Figner, Crone, & Wiers, 2011; Volkow, Fowler, Wang, & Swanson, 2004; Volkow, Koob, Mental, Parity, & Act, 2015).

Over the past two decades, multiple studies have focused on the relationship between chronic substance use and response inhibition, but findings have been equivocal. Inhibitory impairment has been associated with chronic use of some substances (e.g., cocaine, ecstasy, methamphetamine, tobacco, and alcohol) but not for others (e.g., opioids, cannabis, see for a meta-analysis, Smith, Mattick, Jamadar, & Iredale, 2014). Results also vary in studies of

single substances. For instance, heavy drinkers have been reported to make more commission errors than light drinkers on the Go/No-Go task (GNG, Kreusch, Quertemont, Vilenne, & Hansenne, 2014), while alcohol-dependent and control participants did not differ significantly on the same measure (Kamarajan et al., 2005). Two main issues might explain these conflicting findings, namely the phenomenon of polysubstance use and the use of extreme group designs (i.e., comparing control participants and problematic or disordered substance users). In addition, sample demographics and task characteristics are often not taken into consideration. In order to address these issues in this mega-analysis, we aimed to investigate the relationship between inhibition and use of multiple substances by analyzing individual-level data, while taking demographics and task characteristics into account. In doing so, we did not exclusively focus on populations diagnosed with substance use disorders (SUD, American Psychiatric Association, 2013).

1.1.2. Experimental paradigms: the Go/No-Go task and the Stop-signal task

Successful suppression of motor responses can involve distinct behavioral processes such as "action restraint" or "action cancellation" (Schachar et al., 2007). Action restraint refers to stopping a prepared but not yet initiated response, which is commonly measured using the GNG and its variants, such as Conners' continuous performance task (Conners & Sitarenios, 2011; Donders, 1868/1969). These tasks focus on the ability to withhold responding if a no-go stimulus is presented. The main variables of interest are the rate of commission errors (i.e., failures to inhibit a response to no-go targets or false alarms), the rate of omission errors (i.e. failures to respond to go targets, or misses), and the response time (RT) to go stimuli. A relatively high rate of commission errors and a short go RT reflects suboptimal inhibition (Smith et al., 2014).

By contrast, action cancellation refers to stopping a response that is already underway. It is typically measured using the Stop-signal task (SST, Logan, 1994). In this paradigm, each trial starts with the presentation of a go signal that requires an overt response such as a button press. On a subset of trials (typically around 25%), the go signal is followed by a stop signal after a certain interval (stop-signal delay, SSD), upon which participants should inhibit their already initiated go response. Usually, an adaptive tracking algorithm controls the SSD, such that there is a 50% probability of inhibiting the response. A horse-race model, assuming an independent race between the 'go' and 'stop' processes, affords the estimation of the stop-signal reaction time (SSRT, Logan, 1994). Given that the response could not be withheld on *n* percent of all stop trials (usually around at 50%), SSRT is calculated by subtracting the mean SSD from the go RT that marks the *n*th percentile in the go RT distribution.

In contrast to the GNG, the latency of the go response and the latency of the stop process are considered to be independent (Logan & Cowan, 1984). Thus, a longer SSRT reflects an inhibitory deficit, whereas a longer go RT is interpreted as a lack of attention among other influencing factors (preparation, choice, and speed-accuracy trade-off, Lijffijt, Kenemans, Verbaten, & van Engeland, 2005).

In addition to the GNG and the SST, other experimental paradigms, such as the Stroop (Stroop, 1992) and Eriksen Flanker tasks (Eriksen & Eriksen, 1974) have been proposed to measure inhibitory capacities. However, these paradigms measure distractor inhibition rather than motor response inhibition (Nigg, 2000; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). To keep the present review focused and allow for straightforward comparisons of results, we only included studies using the GNG and SST.

1.2. Research Gaps and Research Needs

1.2.1. Previous meta-analyses and reviews

To date, there are at least nine published meta-analyses or review papers examining the relationship between inhibitory control and long-term substance use or behavioral addiction. In terms of scope, these studies can be classified into three categories. First, literature overviews focusing on a single substance (e.g., alcohol: Aragues, Jurado, Quinto, & Rubio, 2011; Stavro, Pelletier, & Potvin, 2013) or non-substance related disorder (e.g., gambling disorder: Chowdhury, Livesey, Blaszczynski, & Harris, 2017; Moccia et al., 2017). These reviews associated alcohol use with prolonged inhibition impairment, up to one month after abstinence (Stavro et al., 2013) and detoxified alcohol-dependent patients showed poor inhibition compared with healthy controls (Aragues et al., 2011). Polysubstance use was not systematically described or controlled for in either of the review studies on alcohol. Individuals with gambling disorder without comorbid SUD were reported to show large inhibition deficits (Chowdhury et al., 2017), which was attributed to impaired activity in prefrontal areas (Moccia et al., 2017). Second, other reviews focused on drawing general conclusions across multiple substances. For instance, Lipszyc and colleagues found that substance users generally did *not* differ significantly from controls in SST (Lipszyc & Schachar, 2010) and GNG performance (Wright, Lipszyc, Dupuis, Thayapararajah, & Schachar, 2014). However, such a review does not provide a clear profile for the effects of these substances in isolation or of specific interactions (i.e., greater than additive or compensation effects). A third category of literature reviews included multiple substances and the results were specified by the substance. Examples include a recent systematic review focused on neuroimaging findings (Luijten et al., 2014) and a meta-analysis focused on behavior (Smith et al., 2014). The latter meta-analysis indicated that inhibitory deficits were apparent for heavy use/disorders related to cocaine, ecstasy, methamphetamine, tobacco,

alcohol, and gambling but not for opioids or cannabis, without testing the interaction effect of using multiple substances (Smith et al., 2014). In sum, the current findings and conclusions of reviews and meta-analyses are rather inconsistent. If a conclusion can be drawn, it appears to be the counterintuitive conclusion that reviews and meta-analyses that focused on a specific addictive substance or behavior are *more* likely to report a significant association with inhibitory control compared to those reporting on multiple substance use. Importantly, none of these reports have considered several key variables that might bias the results, which will be highlighted in the next section.

1.2.2. Important factors to consider

1.2.2.1. Polysubstance use

Polysubstance use broadly refers to the consumption of more than one drug over a defined period, either simultaneously or at different times (Connor, Gullo, White, & Kelly, 2014; Subbaraman & Kerr, 2015). This involves different sub-categories, namely using different substances, the dependence of one substance and co-use of other substances or dependence on multiple substances. For instance, tobacco smoking is strongly associated with alcohol and marijuana use (Connor et al., 2014), opioids, and benzodiazepines are often prescribed simultaneously (Jones, Mogali, & Comer, 2012), and stimulants users are more likely to be heavy drinkers (McCabe, Knight, Teter, & Wechsler, 2005). Note that there is some evidence indicating that concurrent use of substances can lead to additionally toxic effects because of a toxic metabolite, as was reported for alcohol and cocaine (Pennings, Leccese, & Wolff, 2002). It is also possible that the use of one substance decreases the negative effect of another substance, as found with alcohol and cannabis (Schweinsburg, Schweinsburg, Nagel, Eyler, & Tapert, 2011). Hence, studying interactions between drugs on neurocognitive functions is important, given the frequent occurrence and possible interaction

effects. However, studies comparing substance users versus non-users or light users have typically focused on the primary substance of concern, while ignoring secondary substances. Up to now, only a few studies have investigated the relationship between polysubstance use and inhibition (Gamma, Brandeis, Brandeis, & Vollenweider, 2005; Moallem & Ray, 2012; Verdejo-García, Perales, & Pérez-García, 2007). Heavy drinking smokers did not show poorer SST response inhibition than smokers only and heavy drinkers only (Moallem & Ray, 2012). Similarly, ecstasy polysubstance users did not show more strongly disturbed inhibitory brain mechanisms compared with controls (Gamma et al., 2005), and cocaine and heroin polysubstance users showed similar commission error rates as controls in the GNG (Verdejo-García et al., 2007). A limitation of the latter two studies is that the greater-than-additive effect could not be examined without a group of single substance users. The lack of studies calls for a synthesis of research that does take polysubstance use into account.

1.2.2.2. Substance use as a continuous variable

All the above-mentioned reviews and meta-analyses included comparisons between a control or light user group and a heavy or problematic user group. Scores retained as a result of such extreme group designs are often coded and analyzed in terms of low versus high, reducing individual differences into a binary code. This practice involves ignoring individual-differences of substance use in favor of creating quasi-arbitrary groups assumed to be homogeneous on the variable of interest (MacCallum, Zhang, Preacher, & Rucker, 2002; Royston, Altman, & Sauerbrei, 2006; Preacher, Rucker, MacCallum, & Nicewander, 2005). In the current study, we aimed to quantify substance use as a continuous variable.

1.2.2.3. Abstinence

Studies on long-lasting effects of substance use have generally been conducted by testing recently abstinent users. With respect to response inhibition, some studies have found

that abstinence from cocaine, methamphetamine and heroin normalized inhibitory function (Morie et al., 2014; Schulte et al., 2014), however, one study found sustained suboptimal performance after heroin abstinence (e.g., Fu et al., 2008). In addition, the duration of abstinence appears to moderate the return to normal functioning, which may explain these conflicting findings (Schulte et al., 2014). In order to preclude this as a confounder, we did not include studies on abstinence in (formerly) dependent users. All participants indicated substance use in everyday life, but were requested to refrain from using all substances (in most cases excluding tobacco) 24 hrs to one week before testing.

1.2.2.4. Individual-level and task-level variables

Some individual-level and task-level factors are known to affect inhibitory control and are therefore included in this mega-analysis, including the demographic variables age, sex, and education years. For GNG, six task parameters were controlled for: no-go percentage, number of experimental trials, working memory load (taxed or not), substance-related stimuli (used or not), cued GNG or not, and task complexity. For the SST, five task parameters were controlled for: number of experimental trials, stop-trial percentage, SSD settings, stop-signal modality, and SSRT calculation method. Reasons for controlling these confounders are based on a large primary literature on these tasks and are summarized in Supplementary Materials **S1**. Except for sex, for which the interaction with substance use was considered, all other factors were only controlled for regarding their main effect.

1.3. Why a Mega-Analysis Rather Than a Meta-Analysis?

A meta-analysis combines the summary statistics (i.e., effect sizes of included studies), while a mega-analysis combines the raw individual data from different studies. The latter method allows studying the combined effect of individual characteristics (cf. Price et al., 2016) and examining the interaction effect of multiple substances used with enhanced

statistical power (Riley, Lambert, & Abo-Zaid, 2010). Therefore, we implemented a mega-analysis with individual-level data.

1.4. The Goal of the Current Study

Our primary goal was to examine the main and interaction effects of various kinds of long-term substance use on response inhibition. As the interaction effects of substance use on inhibition are rarely investigated and reported, we explore these interactions in the current study. We do so while controlling for demographics (e.g., age, sex, education years) and task-related factors (e.g., no-go percentage, number of trials, whether stimuli are substance-related) that likely explain performance variance between studies and individuals. Interactions between substance use and sex were also included. Based on the literature reviewed above, we tested the following hypotheses: 1) According to Smith et al (2014) and other findings (Colzato, van den Wildenberg, & Hommel, 2007; Fillmore & Rush, 2002, Quednow et al., 2007), we assumed that the inhibitory deficit would be more pronounced in users of psychostimulants (e.g., cocaine, ecstasy, methamphetamine, tobacco, and alcohol), especially for cocaine and amphetamines, given the known neuropsychopharmacology of the cortical and subcortical networks underlying impulse control (i.e., the right dorsolateral and inferior frontal cortices, Koob & Volkow, 2010; Smith, Mattick, Jamadar, & Iredale, 2014); 2) Given the literature, and as a validation of our individual-level mega-analysis, we expect some demographics (e.g., age and sex) and task characteristics (e.g., no-go percentage, whether stimuli are substance-related) to be associated with inhibition performance (see for expected directions of effects, Supplementary Materials **S1**).

2. Method

2.1. Study Identification and Selection

PsycINFO, Medline, EMBASE, Web of Science, CINAHL, and Cochrane Library were searched until 01/03/2016. Search terms and synonyms indicating substance use (alcohol, amphetamine, cocaine, cannabis, heroin, ketamine, methamphetamine, benzodiazepines, gambling, gamer, and internet addiction) were combined with terms indicative of inhibition (go/no-go, inhibitory control, inhibitory process, response inhibition, stop task, etc.). Published meta-analyses and reviews were also checked for additional studies (Horsley, Dingwall, & Sampson, 2011). Although behavioral addictions (e.g., gambling, internet addiction) were initially included, there were too few relevant studies to allow further analyses.

2.1.1. Eligibility criteria

The first author (YL) assessed the eligibility of all records using the following initial inclusion criteria: (a) presented in English; (b) conducted on human participants; (c) reported at least one measure from the following: no-go commission errors or go RT in the GNG; SSRT or go RT in the SST; (d) reported use of at least one kind of substance (e.g., alcohol, tobacco, cannabis, amphetamine, cocaine, ecstasy). Note that we included behavioral data from fMRI/EEG studies if available. In addition, we ran supplementary analyses to investigate whether inhibition performance varied with study type (behavioral/EEG/fMRI). It turned out that study type did not systematically influence behavioral performance (see Supplementary Materials **S2**). We excluded studies (a) that presented stop signals using a single SSD, as this is known to induce a performance strategy of delayed responding (Logan, 1994); (b) in which the percentage of no-go or stop trials was higher than 50%, as this is known to invalidate the task (Nieuwenhuis, Yeung, & Cohen, 2004; Randall & Smith, 2011);

(c) that focused on the acute effects of substances on inhibition; (d) that recruited participants with a family history of substance dependence; (e) that excluded polysubstance users; (f) with participants that already received treatment for SUD or abstained from substance use; (g) with participants younger than 18. The exclusion of both intoxicated and abstinent consumers may have kept heavily affected/addicted participants from being included in the sample.

After applying the inclusion and exclusion criteria by YL, a second rater (author YG) assessed the eligibility of a random subset (20%) of the records and obtained 100% agreement. Authors of eligible studies were invited via email to contribute raw data. Repeated attempts were made (i.e., four reminders were sent) if no response was received. Corresponding authors of the identified studies were asked to share their raw individual data, following our instructions on data requirements. The 'essential variables' included a set of pre-identified variables, including sociodemographic characteristics (e.g., age, sex, and education), typical alcohol and tobacco use (as alcohol and tobacco are two most commonly used substances), and task performance (**Table S1a, S1b**). 'Optional variables' (Supplementary Materials **S3**) included other demographic information recorded (e.g., race), other substance use (e.g., cocaine, cannabis) and questionnaires administered (e.g., Alcohol Use Disorder Identification Test (AUDIT), Saunders, Aasland, Babor, De la Fuente, & Grant, 1993). The 'optional variables' were defined in a more flexible format with open questions. A study was included in our mega-analysis only if information about all 'essential variables' could be provided.

2.1.2. Quality assessment and data extraction

As the quality of included studies can influence mega-analysis in unpredictable ways (i.e., shortcomings in original studies will be carried over to the mega-analysis and thus weaken its conclusions, Müller, Brändle, Liechti, & Borgwardt, 2019), a quality assessment

of original studies was conducted. The methodological quality of studies was assessed by two authors (YL and YG) separately. We used the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, which is widely used and recommended by Cochrane for quality assessment of observational and cross-sectional studies (**Table S2**, National Heart and Blood Institute, 2014). The total agreement (Good/ Fair/Suboptimal) between assessors was high (GNG: 20/24 = 83%, SST: 16/20 = 80%). Inter-rater reliability, measured using Spearman's rank correlation coefficient was high for GNG ($r = 0.84$, $p < 0.001$) and moderate for SST ($r = 0.56$, $p = 0.01$, Kendall, 1938).

All provided data, including predictors (i.e., substance use, demographics, task characteristics) and dependent variables were merged into four datasets separated based on the four dependent variables (i.e., the commission error rate in GNG, go RT in GNG, SSRT in SST, and go RT in SST. As speed-accuracy trade-off is a potential issue in GNG (Zhao, Qian, Fu, & Maes, 2017), a balanced integration score was calculated (Liesefeld & Janczyk, 2019). Main results applying this score as the outcome are presented in Supplementary Materials **S4**. The first author performed the data merging, which was verified by two authors (RW and WW).

2.1.3. Publication bias check

To examine whether significant findings in the original papers are indicative of evidential value, a *p*-curve was calculated and plotted (Simonsohn et al., 2015). In a *p*-curve, the x-axis represents *p*-values below 0.05, and the y-axis represents the percentage of studies yielding such a *p*-value. A right-skewed *p*-curve indicates evidential value, whereas a left-skewed *p*-curve, many *p*-values just below 0.05, may be indicative of flexibility in data analysis (Simonsohn et al., 2015). If the data did not indicate evidential value, a 33% power

test is performed to examine whether the absence of evidential value is due to insufficient power. A *p*-curve disclosure table was added in Supplementary Materials (**Table S3**) according to Simmons and Nelson (2015). *P*-curves and corresponding analyses were conducted using the *p*-curve app 4.06 (http://www.p-curve.com/app4, 2018).

2.2. Individual Participant Data Meta-Analysis

The analysis was conducted in the following steps: 1) apply additional exclusion criteria to the merged datasets; 2) standardize all continuous independent variables; 3) determine substance-related one-way variables; 4) dummy code all discrete variables; 5) determine and generate substance-related interaction variables; 6) multiple imputations of the missing values using all main and interaction variables; 7) build the linear mixed regression model with fixed effects of all predictors and a random intercept; 8) variable selection by stepwise backward elimination. These eight steps are outlined in more detail below.

2.2.1. Construction of the database

2.2.1.1. Individual and group exclusion criteria

The data from the included studies were stacked into a single data file for each dependent variable, with unique identifiers for each study and for each participant. We further applied some minimal exclusion criteria to the individuals. That is, we excluded a participant if (1) he/she was younger than 18 years old; (2) he/she had missing data on all indices of substance use; (3) the dependent variable of current analysis (e.g., commission error rate) was missing; (4) SSRT was negative.

A group of substance users from a certain study was excluded if the substance was not included as a predictor in the model. This happened when there was limited data provided for that substance (see criteria in 2.2.1.3.1.). For example, if it was concluded that opiate use was assessed insufficiently across all studies, we did not add opiate as a predictor. Consequently,

opiate users were excluded from the analysis. The excluded cases and groups from each study are listed in **Table 1** and **Table 2**.

2.2.1.2. Standardization of independent variables

2.2.1.2.1. Continuous variables

Demographics like age and education level were transformed respectively into continuous variables years and years of education according to the education system in the country where the study was conducted. Task characteristics such as no-go percentage and number of trials in both tasks were also treated as continuous variables.

Alcohol consumption was converted into the continuous variable grams of ethanol per month. Data on alcohol consumption were provided in two different ways. Most researchers provided data based on timeline follow-back (TLFB). These data were either already in grams per month or could be transformed by making use of standard drinks adjusted for country (Cooper, 1999). Some studies only had data from more general questionnaires. For instance, three studies (de Ruiter, Oosterlaan, Veltman, van den Brink, & Goudriaan, 2012; Luijten, O'Connor, Rossiter, Franken, & Hester, 2013; Rossiter, Thompson, & Hester, 2012) provided the raw data of the AUDIT (Saunders et al., 1993). In that case, we multiplied midpoints of item 1 (frequency), midpoints of item 2 (drinking days per month) and standard drinks in the country where the study took place. Similarly, four studies (Littel et al., 2012; Luijten et al., 2011; Luijten, Meerkerk, Franken, van de Wetering, & Schoenmakers, 2015; Luijten et al., 2013) provided Quantity Frequency Variability (QFV) score (Lemmens, Tan, & Knibbe, 1992). Again, items of quantity, frequency, and standard drinks were multiplied together. Smoking was coded as cigarettes per day. Two studies (Moallem & Ray, 2012; Rossiter et al., 2012) only had data from the Fagerström Test for Nicotine Dependence (FTND, Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). In these cases, the midpoint

of the answer to item "How many cigarettes a day do you smoke" was used for daily cigarette use. One study used a self-developed 7-point Likert scale for the past 6 months tobacco consumption, for which we estimated daily cigarette use with the midpoint scores (Ames et al., 2014). Alcohol and tobacco use were standardized across the full dataset. All the other substance use variables had to be treated as dichotomous variables, as insufficient information was provided for treating it as a continuous variable in the model (see details below).

2.2.1.2.2. Dichotomous variables

For interpretability, dichotomous variables were effect-coded with value +1 or -1. Except for alcohol and tobacco use, other substances were coded as 'lifetime use (yes = 1/no = -1)'.

Four dummy task-characteristics were defined to classify the GNG studies: 'working memory load (low/high)', 'substance-related (yes/no)' 'cued GNG (yes/no)', and 'task complexity (low/high)'. High working memory load, substance-related, cued GNG versions and complicated tasks were assigned the value of 1 (otherwise -1). Tasks with high working memory load were also assigned a value of 1 for task complexity as the association between stimuli and response was more complicated in these tasks.

Similarly, for the SST, three dummy task characteristics were extracted, including 'stop-signal modality (visual/auditory)', 'SSD (fixed/staircase-tracking)' and 'SSRT calculation (integration/others)'. These variables were assigned a value of 1 if auditory stop signals were used; staircase-tracking procedure for SSD; and integration method for SSRT calculation (otherwise -1).

2.2.1.3. Identification and generation of substance-related variables

Except for alcohol use and tobacco use, other kinds of substances had missing data as not all studies provided information. Data provided varied in the level of detail, the way questions were asked, and the substances of main interest. For instance, depending on the primary substance of interest, some studies provided detailed information for cannabis use but no information on cocaine use (Bidwell et al., 2013), with an opposite pattern for others (Colzato, van den Wildenberg, & Hommel, 2007). In the following section, we explain the criteria for including substance-related variables in the model.

2.2.1.3.1. One-way variables

Due to missing data, a criterion was needed to include a variable in the model. We decided on a minimum of 100 participants per cell for a substance (which comes down to a power of 0.94 for the effect size of 0.5). As a result, final models for the GNG (both commission error rate and go RT) included cannabis, cocaine, amphetamine, ecstasy, and hallucinogens, in addition to alcohol and tobacco. For the SST (both SSRT and go RT), the final models included cannabis, cocaine, and ecstasy in addition to alcohol and tobacco.

2.2.1.3.2. Two-way variables

There were two types of two-way variables; the interaction of sex × substance and substance1 × substance2. Variables of sex × substance were created by multiplying sex with substance directly. For the second type, in order to evaluate whether there was sufficient data to assess these interactions, we again applied a criterion for inclusion. For example, dummy coding cannabis and cocaine use yielded a two by two table

cannabis (yes/no) × cocaine (yes/no). The corresponding interaction was only entered into the model if all four cells had more than 20 entries. For alcohol and tobacco use, we dichotomized the data by a median split for table construction only. We performed an

additional analysis to test whether the number of substances used was a predictor of inhibition performance, and this was not the case (see Supplementary Materials **S5**). The list of included two-way variables can also be found in Supplementary Materials (**Table S4a-S4d**). Demographics (in addition to sex) and task parameters could further moderate the relationship between substance use and inhibition. This, however, was not the focus of the current paper. In order to explore this potential issue, we analyzed interactions between alcohol on the one hand and demographics and task parameters on the other (see Supplementary Materials **S6**).

2.2.1.3.3. Three-way variables

Three-way variables were generated based on the substance1 × substance2 variables combined with sex. The corresponding variables were entered into the model only when all the eight cells in the three-way table
sex (male/female) × substance1 (yes/no) × substance2 (yes/no) consisted of at least 10 entries. The list of three-way variables can be found in Supplementary Materials (**Table S4a-4d**).

2.2.2. Missing data for independent variables and their interactions

In the analysis of GNG commission error rate, the percentage of missing values ranged from 0 to 68.2% (highest: alcohol × hallucinogens × sex) and in the GNG go RT analysis, it ranged from 0 to 69.6% (highest: alcohol × hallucinogens × sex). For the SST, the percentage of missing values ranged from 0 to 84% for the SSRT
(highest: tobacco × ecstasy × sex) and from 0 to 83.2% for the go RT (highest:
tobacco × ecstasy × sex, a full list of missing data per variable can be found in **Table S4a-s4d**).

In order to deal with these missing data, we used multiple imputations (Rubin, 2004). The default imputation option in SPSS was chosen. It first scans the data and determines the

suitable method for imputation (Monotone or Fully Conditional Specification, FCS; Dong & Peng, 2013). All variables in the mixed regression model, including the main and interactive predictors and the dependent variable, were used for imputation. Apart from that, the discrete variable of 'tobacco lifetime use' was also used, as some studies assessed tobacco use dichotomously (smokers/non-smokers). It has been suggested that the number of imputations should be similar to the percentage of cases that are incomplete (White, Royston, & Wood, 2011) and the precision improves by increasing the number of imputations (Bodner, 2008). Therefore, 100 complete data sets were generated, which were combined into a pooled result using the method proposed by Rubin (Rubin, 2004) and Schafer (Schafer, 1997).

2.3. Statistical Analysis

Backward elimination was used for variable selection. Initially, each imputed dataset was analyzed with a linear mixed model including all the above-mentioned main, second order, and third order effects as fixed effects and a random intercept (for which a model summary can be found in **Tables S4a-S4d**). We did not include random slopes and thus assumed that predictors had similar effects in each study. The fixed effects that were least significant (i.e., the one with the largest *p*-value) were removed and the model was refitted. Each subsequent step removed the least significant variable in the model until all remaining variables or its higher order variables had *p*-values smaller than 0.05 (Draper & Smith, 2014). For instance, if the variable alcohol × tobacco was significant, then variables of alcohol and tobacco would also be included in the model, irrespective of their independent significance.

3. Results

3.1. Study Selection

3.1.1. Summary of authors' responsiveness

Applying the inclusion and exclusion criteria resulted in a sample of 153 potentially eligible studies (**Fig. 1**). Out of these targeted papers, 4 researchers responded that they no longer had access to the datasets, 21 declined to participate, 52 did not respond to our invitation and 11 did not have all the basic information we asked for. In total, we obtained raw data from 65 studies. Out of these, 22 had to be excluded because the authors could not provide all the 'essential variables', such as data on monthly alcohol use in grams was unavailable (9 studies), missing data of tobacco use (5 studies), participants were abstaining from substance use (3 studies), participants were younger than 18 years old (2 studies), uncommon tasks were used (2 studies) and unsuitable outcome measures (1 study, provided stop latency instead of SSRT). The full list can be found in Supplementary Materials **S7**. The final dataset for the GNG comprised of 23 independent datasets from 24 papers (in some cases, more than one paper was published with the same dataset). For the SST, 19 datasets from 20 papers were included. In addition, one study administered both GNG and SST; therefore 43 unique studies were included in total.

The final list of eligible studies was slightly different from the list of studies included in Smith and colleagues meta-analysis on summary statistics (Smith et al., 2014). For the GNG, there were 11 studies in common. For the SST, there were 6 studies in common. These discrepancies were related to different research questions. Since we aimed to assess the unique and combined effects of different substances, while Smith and colleagues focused on the unique effect of a single substance, some studies that were excluded by Smith and colleagues were included here and vice versa. In addition, individual data mega-analysis typically has a lower response rate compared to traditional meta-analysis, as it requires more work from the researchers (Riley et al., 2010; Riley, Simmonds, & Look, 2007).

3.1.2. Study description

Table 1 and **Table 2** present descriptive characteristics of the included GNG and SST studies before imputation, respectively.

3.1.3. Findings in original studies

For GNG, out of the 24 studies included, 9 (37.5%) reported that (heavy/problematic) substance users/excessive gamers made more commission errors than controls/light users (3 for alcohol, 2 for tobacco, 1 for ecstasy, 1 for inhalant and 2 for excessive gamers), 1 (4.2%) reported opposite findings (i.e., opiate users made fewer commission errors compared to controls), 11 (45.8%) reported no significant differences (5 for alcohol, 2 for tobacco, 1 for ecstasy, 1 for inhalant and 2 for polysubstance use), and 3 (12.5%) didn't have such an analysis (See **Table 1** footnote). For the SST, out of the 20 studies, 5 (25%) reported substance users/gamblers had longer SSRT than controls (2 alcohol, 2 cocaine and 1 pathological gambling), 1 (5%) reported the opposite direction (alcohol), 8 (40%) reported no difference (3 alcohol, 2 tobacco, 1 cannabis, 1 cocaine, and 1 pathological gambling) and 6 (30%) did not provide such an analysis (see **Table 2** footnote).

3.2. Quality Assessment

We rated the methodological quality of the studies according to the NHLBI assessment tool (see **Tables 3a and 3b**). For the GNG, most (58.3%) of the studies were of intermediate quality, 37.5% of high quality and 4.2% of suboptimal quality. For the SST, 40% of studies were of high quality and another 60% of intermediate quality. The main limitations were small sample size, especially for the studies focused on neuroimaging findings, and insufficient control of confounders such as the history of other kinds of drug use. For a few studies, the population was not fully described, lacking information of where and when the participants were recruited. To explore whether different study types differ in methodological

quality, we did a chi-square test based on **Table 3**. The results indicate that the percentages of studies of *good, fair and suboptimal* quality did not differ between behavioral (10/23, 13/23, 0/23), EEG (4/8, 3/8, 1/8) and fMRI (3/12, 9/12, 0/12) studies (χ^2 (4, N = 44) = 6.51, p = 0.15).

3.3. Publication Bias Check

To examine evidential value in the original studies, a *p*-curve was created (Supplementary Materials **Fig. S1**). Out of the 31 effect sizes (unavailable for some studies), 11 were statistically significant ($p < 0.05$), with 8 $p < 0.025$. The *p*-curve analysis on the association between substance use and response inhibition indicated no evidential value (full *p*-curve $z = -0.98$, $p = 0.16$; half *p*-curve $z = 0.58$, $p = 0.72$). However, this was likely due to a lack of power (33% power test, full *p*-curve z = -0.95, $p = 0.17$).

3.4. Main Outcomes

3.4.1. GNG: no-go commission errors

None of the substance-related variables or their interactions had a significant effect on the commission error rate. Among all other variables, two demographic variables and three task characteristics significantly predicted commission error rates. Age significantly predicted commission error rate ($\beta = -0.01$, $p < 0.01$, 95% CI [-0.02, 0.00]), indicating that older participants showed decreased commission error rates. Education years also significantly predicted commission error rate ($\beta = -0.01$, $p = 0.03$, 95% CI [-0.02, 0.00]), indicating the higher the educational level, the lower the commission error rates. The nominal variable working memory load had a significant effect on commission error rate ($\beta = 0.10$, $p < 0.01$, 95% CI [0.07, 0.14]), indicating that when working memory load was high, participants made more commission errors. The no-go percentage had a significant effect on commission error rate ($\beta = -0.04$, $p < 0.01$, 95% CI [-0.07, -0.02]), such that the higher the no-go percentage,

the lower the rate of commission errors. The number of trials also had a significant effect on commission error rate (β = 0.04, p < 0.01, 95% CI [0.02, 0.07]), indicating higher commission error rates when there were more trials.

3.4.2. SST: SSRT

Lifetime cannabis use significantly predicted SSRT, with users showing longer SSRT than non-users (β = 5.59, p = 0.03, 95% CI [0.41, 10.77]). Tobacco use was positively, although not significantly, associated with SSRT (β = 3.21, p = 0.06, 95% CI [-0.13, 6.55]), indicating that the more tobacco was consumed, the longer SSRT. The tobacco × cannabis interaction also had a significant effect on SSRT (β = -4.19, p = 0.03, 95% CI [-8.03, -0.37], **Fig. 2**). Post-hoc analyses were performed by splitting the imputed data sets and fitting the same restricted model without the interaction term. These analyses revealed that for the cannabis non-users, higher tobacco use was associated with longer SSRT (β = 6.44, t = 2.70, p < 0.01). For cannabis users, no effect of tobacco use on SSRT was observed (β = -0.15, t = -0.05, p = 0.96). When split based on cigarette smoking (median-split of z-score), the following effects were obtained: for low tobacco users, cannabis lifetime users did not differ significantly from cannabis non-users in SSRT (β = 7.62, t = 1.90, p = 0.06). A similar finding was observed among high tobacco users (β = 4.80, t = 1.74, p = 0.08).

Education years also significantly predicted SSRT (β = -9.33, p < 0.01, 95% CI [-12.88, -5.80]), indicating that the higher the education level, the shorter the SSRT. Age significantly predicted SSRT (β = 13.46, p < 0.01, 95% CI [9.29, 17.63]), with an increase in SSRT along with an increase in age. The number of trials also significantly predicted SSRT (β = -17.44, p < 0.01, 95% CI [-30.60, -4.28]), indicating a decrease in SSRT when there were more trials. In addition, stop-signal modality had an effect on SSRT (β = -28.58, p = 0.01, 95% CI [-50.61, -6.56]), indicating that auditory stop signals induced shorter SSRT

compared to visual stop signals. SSD also had a significant effect on SSRT (β = -33.29, p = 0.04, 95% CI [-64.61, -1.96]), indicating that the staircase-tracking procedure resulted in shorter SSRT compared to the fixed SSD procedure.

For both SSRT and commission error rate, models including the interaction between alcohol use on the one hand and demographics and task parameters on the other resulted in largely comparable findings as presented here[1]. Only in the GNG, an interaction between alcohol use and age appeared (β = 0.01, p = 0.02, 95% CI [0.001, 0.02]). For light drinkers, older people made less commission errors (β = -0.02, t = -2.56, p = 0.01), which was in line with the main effect of age. Whereas for heavy drinkers, this relationship was absent (β = -0.01, t = -1.50, p = 0.14). All other interactions with alcohol were found to be non-significant (Supplementary Materials **S6**).

Outcomes for go RT in GNG and SST can be found in Supplementary Materials **S8**. Briefly, older people had longer go RT in both GNG and SST. Higher educated people had shorter go RT in SST. Although the interaction between cocaine and tobacco had an effect on go RT in SST, post-hoc analysis revealed no significant simple effect.

4. Discussion

Previous individual studies, reviews, and meta-analyses investigating inhibitory control deficits in relation to long-term substance use and SUD have provided mixed results (Luijten et al., 2014; Smith et al., 2014; Wright et al., 2014). These inconsistent findings might at least partly be due to insufficient control of frequently occurring polysubstance use. In addition,

[1] In the model including interactions with demographics and task-parameters, tobacco and cannabis use were both positively associated with SSRT. However, their interaction was not significant, but the three-way interaction with sex was. Post-hoc tests indicated that, only for male non-cannabis users, tobacco use was positively associated with SSRT (see in Supplementary Materials **S6**).

studies differed in sample demographics and task-related variables and used extreme group designs. The current mega-analysis aggregated data of 3610 individuals, from 43 studies, in which polysubstance use, demographics, and task parameters were included in the prediction of inhibition performance by means of an imputed multilevel analysis. Most of the included studies were of medium to high quality, which validates the overall conclusions drawn. Surprisingly, our overall pattern of results indicated that most types of substance use did not show an association with response inhibition. While for most substances no effects were found, lifetime cannabis use was found to be associated with impaired inhibition, as indexed by an increased SSRT in the SST. Tobacco use was also associated with impaired inhibition as indexed by the same variable. In addition, an interaction between lifetime cannabis and tobacco use was found on SSRT, which indicated a strong positive relationship between daily tobacco use and SSRT in participants who did not use cannabis (indicating poorer inhibition), and the absences of such a relationship in users smoking cannabis. In addition, demographic factors such as age and years of education and task characteristics such as no-go percentage, affected inhibition performance in the expected direction, strengthening the credibility of the other results.

4.1. Response Inhibition and Substance Use

The main significant finding of our mega-analysis was that lifetime cannabis use was associated with prolonged response inhibition in the SST. One possible explanation is that this could (partly) involve subacute effects of cannabis use (i.e. lasting 7 hours to 4 weeks after last cannabis use, Gruber & Yurgelun-Todd, 2005; Pope & Yurgelun-Todd, 1996; Schulte et al., 2014). Acute cannabis use (i.e., 0-6 hours after last cannabis use) has been consistently reported to impair response inhibition in the SST (Metrik et al., 2012; Ramaekers et al., 2006). In contrast, findings of its long-term effect (i.e., 3 weeks or longer after last cannabis use) were mixed (Crean, Crane, & Mason, 2011), with some confirming an

impairing effect (Moreno et al., 2012), while others did not (Tapert et al., 2007). To have a closer look at the effect of cannabis, we compared cannabis daily users with less frequent users. A linear mixed regression model was built with the fixed effect of 'cannabis daily users (yes/no)' and a random intercept. It indicated that cannabis daily users did not differ from less frequent users on their stopping latency (i.e., SSRT., β = -6.42, p = 0.90, 95% CI [-114.27, 127.10]), which does not support the hypothesis of subacute cannabis effects. Despite conflicting behavioral findings of the relationship between cannabis use and response inhibition, abnormalities in neural activation have often and more consistently been reported in relation to acute as well as chronic cannabis use compared with non-users (systematic review: Wrege et al., 2014). Age of onset may have a moderating effect on the neural effects of cannabis (Hester, Nestor, & Garavan, 2009), but we did not have sufficient data to test this hypothesis.

In line with previous findings, tobacco use tended to impair inhibition. Participants with a higher level of tobacco dependence demonstrated a lower level of response inhibition capacities (Billieux et al., 2010), and smokers performed worse than non-smokers in a smoking-related GNG (Luijten et al., 2011). However, it should be noted that the main effect of tobacco use was qualified by a significant interaction with cannabis use, indicating a negative effect of tobacco use only in non-cannabis users. Another study reported that co-administration of cannabis and tobacco attenuated the impairment in delayed recall memory caused by cannabis alone (Hindocha, Freeman, Xia, Shaban, & Curran, 2017), and other reports have indicated weaker impairment on some measures after polysubstance use (e.g., alcohol and cannabis, Schweinsburg et al., 2011). One possible interpretation of these findings is that cannabis has a protective effect when used together with other substances such as alcohol and tobacco (cf., Viveros, Marco, & File, 2006). Due to the high co-occurrence of cannabis and tobacco use (Badiani et al., 2015; Leatherdale, Ahmed, &

Kaiserman, 2006), and the fact that concurrent tobacco use contributes to cannabis dependence symptoms (Ream, Benoit, Johnson, & Dunlap, 2008), further studies of the combined and single effects on response inhibition are warranted to elucidate these findings.

What could explain the low evidence for a relationship between (most) long-term substance use and inhibition? On closer inspection, only 30% of studies included reported evidence for negative associations between substance use (or gambling) and response inhibition (**Tables 1 and 2**). In contrast, other studies reported evidence for positive associations between substance use and inhibition performance in GNG and SST (significant: Glass et al., 2009; nonsignificant: Galván, Poldrack, Baker, McGlennen, & London, 2011; Papachristou, Nederkoorn, Havermans, van der Horst, & Jansen, 2012; Vonmoos et al., 2013). In light of this, it is less surprising that the integrated results indicated overall largely null findings (most of the confidence intervals ranged around zero). Similarly, only one out of the five studies included in a recent review (Carbia, López-Caneda, Corral, & Cadaveira, 2018) reported impaired response inhibition—as measured by SST and GNG tasks—in binge drinkers compared with controls (Czapla et al., 2015).

One explanation is that chronic recreational substance use without a diagnosis of SUD is not associated with response inhibition impairment. In other words, a threshold effect rather than a linear effect might exist between substance use and response inhibition performance. Alternatively, there might be a linear relationship, albeit shallow and we only see the effects when comparing very extreme groups (e.g., healthy controls vs. SUD in clinical samples). As a result of our exclusion criteria, **Fig. S2a** and **S3a** indicate that only a minority of the participants reached the level of SUD (either reported in individual paper or categorized based on questionnaire score), and most others were still within the normal range of use. It is conceivable that inhibition is only impaired in SUD (Bjork, Hommer, Grant, & Danube, 2004; Fernández-Serrano, Pérez-García, & Verdejo-García, 2011; Noël et al., 2007;

Petit et al., 2014). Alternatively, inhibition problems may play a role in the transition from heavy use to SUD. In the SST sample, there were more people diagnosed with tobacco dependence (about 10%, **Fig. S3a**), which might explain why a positive (although not significant) association of SSRT and tobacco use was found.

A second possibility is that substance use is actually associated with impaired inhibition, but we were unable to detect this. Possible reasons include: sample characteristics (as was discussed in the last paragraph), the type of tasks included, outcome measures (i.e., effects may only be visible in biological markers but not in behavior), and statistical power. Regarding *tasks included*, there is the possibility that (heavy) use of psychoactive substances does not lead to a general inhibition problem, but only to a specific problem in the domain of substance use (hence an interaction between an appetitive process and suboptimal control, Jones, Duckworth, Kersbergen, Clarke, & Field, 2018). A related explanation can be that self-control failures like maladaptive substance use may reflect a reduced mobilization of inhibitory control in substance-related contexts rather than generally impaired inhibitory control competencies (Krönke et al., 2018; Krönke, Wolff, Benz, & Goschke, 2015; Wolff et al., 2016). However, in a secondary analysis, we did not find that substance-related GNG moderated the relationship between alcohol and commission error rate (see details in **4.2.**). Furthermore, the SST and GNG measure stimulus-driven (exogenous) inhibition, which may not closely match real-world 'loss of control' behavior related to substance use (e.g., an initial intention to have one drink escalating into a binge-drinking session, failed suppression of craving, etc). These examples reflect a different type of inhibition, namely endogenous or intentional rather than exogenous inhibition. Intentional inhibition paradigms such as the Marble task (Schel et al., 2014) could be considered in future research. Regarding *outcome measures*, it is possible that biological but not behavioral markers might be more sensitive to inhibition impairments among substance users (Garrison & Potenza, 2014). Relatedly, some

of the included MRI studies reported specific group-related abnormalities in brain activation but not in behavioral outcomes (e.g., Claus, Ewing, Filbey, & Hutchison, 2013; de Ruiter et al., 2012; Galván, Poldrack, Baker, McGlennen, & London, 2011; Karoly, Weiland, Sabbineni, & Hutchison, 2014; Luijten et al., 2013; Roberts & Garavan, 2010). In addition, a recent study indicated that resting state fMRI connectivity might serve as a promising biomarker of alcohol use disorder severity (Fede, Grodin, Dean, Diazgranados, & Momenan, 2019; see further, Steele, Ding, & Ross, 2019 for additional recent approaches to identifying biormarkers for addiction). Alternatively, Kwako, Bickel, and Goldman (2018) suggested a dimensional approach to biomarkers in terms of executive functions (inhibitory control, working memory, etc.), which includes measuring neuropsychological tests and epigenetic changes in relevant genes (e.g., COMT). With respect to *statistical power,* polysubstance use was coarsely defined, such that substances other than alcohol and tobacco had to be coded in a binary lifetime use variable. It is still possible that (heavy) use of a specific combinations of substances at the same time (e.g., cocaine and alcohol, Schulte et al., 2014) does have a negative impact, which did not emerge from our analysis here using binary variables. In addition, the total author response rate was low, which we discuss as a limitation. Currently, it remains an open question whether substance use is not associated with a motor inhibition impairment or if we were incapable of detecting such an impairment.

4.2. Demographics and Task Parameters

Our results indicate that age is a significant predictor of performance. In the GNG-task, the age-related increase in accuracy is most likely due to the strategic slowing of responses (confirmed by longer go RTs). In the SST, SSRT increased with age. Education was positively correlated with inhibition capability in both tasks. There was not a significant effect of sex on inhibition, nor any interactions between sex and substance use. In the GNG, higher working memory load, lower no-go percentages, and a higher number of experimental

trials resulted in more commission errors. These effects are in line with the primary literature on these tasks and are further discussed in Supplementary Materials **S1**. Somewhat surprisingly, we did not obtain an effect of substance-related GNG on performance measures compared to classical task versions. This is in line with a recent meta-analysis, where the main effect of appetitive cues was not observed after correction for publication bias, and where drinking status (light vs. heavy drinkers) also did not moderate this effect (Jones, Duckworth, Kersbergen, Clarke, & Field, 2018). In a small exploratory analysis, we examined the alcohol × substance-related task interaction effect, which was not a significant predictor of commission error rates in GNG (Supplementary Materials **S6**). Still, since our conclusion is based on only 5 out of 23 included studies, future research should address this question. In the SST, visual (vs. auditory) stop signals, fewer number of trials and fixed SSDs (vs. staircase-tracking procedure) induced prolonged SSRT (elaboration in Supplementary Materials **S1**).

4.3. Implications

Our results showed no relationship between the use of most substances and impaired response inhibition, except for a relationship between cannabis use and impaired inhibition, and in non-cannabis users an association between cigarette use and impaired inhibition. What are the theoretical implications? First, these findings could be of relevance for the current debate on the question whether addiction should be considered a chronic brain disease or not (Heather et al., 2017; Leshner, 1997; Field, 2015; Volkow, Koob, Mental, Parity, & Act, 2015). The current findings do not support the idea that long-term recreational substance use leads to irreparable problems in inhibition, although it cannot be excluded that inhibition problems are present in (a subgroup of) people diagnosed with SUD. Second, in many dual process models of addiction, suboptimal inhibition of stimulus-driven appetitive processes (cue-reactivity) plays an important role in the escalation of use (e.g., Baler & Volkow, 2006;

Wiers et al., 2007). An alternative perspective does not emphasize the competition between stimulus-driven and goal-directed processes, but rather between different goal-directed processes (Moors, Boddez, & de Houwer, 2017). Individuals learn to mobilize and allocate resources strategically according to goal saliency and importance (Köpetz, Lejuez, Wiers, & Kruglanski, 2013). In this way, the inhibition capability of substance users is expected to fluctuate moment-to-moment (i.e., state-like) based on the external and internal context. Note again that the current findings do not exclude the possibility that in severe addiction(s), chronic inhibition problems of stimulus-driven processes do play a role. It merely underscores the goal-directed nature of (heavy) substance use. Third, impaired response inhibition as an immediate consequence of substance consumption may be more important than general inhibitory impairments in the long term. Compared with long-term (non-dependent)substance use, acute use is more consistently related to impaired inhibitory control that enhances further consumption (Gan et al., 2014).

4.4. Limitations and Suggestions for Future Study

There are several limitations of the current study worth considering. First, the response rate was rather low. Although more than 100 studies met our inclusion and exclusion criteria, authors of only 65 studies provided raw data. The reasons for this include inaccessibility of the data, data could not be shared due to regulations, and a lack of success in contacting the authors. The low response rate is an obstacle encountered commonly in mega-analyses (Riley et al., 2010, 2007). We calculated and compared the effect sizes of studies that were included, studies that provided data but that were not included, and studies did not provide data. It was found that these three kinds of studies did not differ significantly on effect size (**Fig. S4**, see statistics in Supplementary Materials **S9**). In light of this, an open science framework is recommended in order to increase the transparency and availability of data for future research. Despite these obstacles, we received raw data from 3610 participants,

which should provide sufficient power to test effects on inhibition of substance use. Second, and relatedly, we noticed that the original studies did not score the use of every substance, for example, data on opiates were scarce. Although we tried to remedy this by means of multiple imputations, the analyses on the effects of these substances might have been underpowered. Third, except for alcohol and tobacco use, other substances could only be coded as a binary 'lifetime use' variable. It would be optimal if a standard way of assessing all substances could be used in the future when assessing the relationship between substance use and inhibition (or other neuropsychological functions). Guidelines for experimental protocols and assessment of substance use would facilitate future multicenter comparisons, which could be stimulated by funding agencies requiring a standard assessment of all commonly used substances in a uniform format. Fourth, studies did not focus on poly-substance use. Studies recruited individuals taking one substance and recorded one/several other substances. Therefore, the samples are highly selective and not representative of poly-substance users. In addition, future studies are suggested to include a standard index of trait impulsivity (e.g., Eysenck's personality inventory, Eysenck & Eysenck, 1965; BIS-11, Patton, Stanford, & Barratt, 1995) as it is possible that within-sample variability on this dimension is obscuring common effects of drug exposure, or has stand-alone effects, especially for stimulant users (Ersche et al., 2012). Last, the effects of age and education years should be considered in the analysis and explanation of results. Task characteristics like stop trial percentage that consistently influence task performance should also be considered when comparing across studies.

5. Conclusions

The current mega-analysis aggregated raw data from 3610 participants in 43 studies on long-term (mostly) light to moderate substance use and response inhibition. The main finding is that limited evidence was found for impaired response inhibition in substance users, with two exceptions: lifetime cannabis use, and cigarette smoking in people who do not use

cannabis. The validity of these findings is underscored by expected findings for demographics (e.g., age, education level) and task characteristics (e.g., stop percentage). Broad assessment, standardized recording and reporting of substance use are highly needed in future studies.

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Figure captions

Figure 1: PRISMA for the mega-analysis detailing our search and selection decisions.

Figure 2: The interaction between cannabis and tobacco use on SSRT. Only for cannabis non-users, the more tobacco a person smoked on a daily basis, the longer his/her stopping latency. For cannabis users, a mild positive association was found between tobacco use and SSRT.

Table 1

Description of included GNG studies (dependent variable is commission error rate)

Study	Demographic information				substance of use			Task characteristics						Dependent variables			N ex (i w
	Sample size (reserved)	Age M (SD)	Males %	Education years M (SD)	Main substance in the original paper	criteria for the heavy/problematic substance use group	Other substance use info provided	Trial number	No-go percentage	Substance related	Working memory load	Task complexity	Cue GNG	No-go commission error	Go RT M (SD)	Main behavioral findings	
Ames et al, (2014)	41	20.46 (1.27)	41	Missing	Alcohol	21 heavy drinker with AUDIT score>8, binge drink > twice/week and 15 drinks (female 8)/week		200	20	Yes	No	Yes	No	10 (6.22)	439(48)	There was no difference between light and heavy drinker on commission error rate, and mean go RT	
Claus et al, (2013)	144	32.64 (9.65)	69	14.2 (2.25)	Alcohol	81 participants were diagnosed with alcohol dependence according to DSM-5		624	6.41	No	Yes	Yes	No	59 (16.37)	335(59)	There was no correlation between alcohol use disorder severity and inhibition performance	
Hendershot et al, (2015)[a]	83	19.86 (0.81)	48	12.99 (1.34)	Alcohol	All participants at least binged drink once in the past month.	Cannabis, cocaine	62	20	No	No	No	Yes	7 (7.8)	315(28)	Response inhibition was worsened following the rising limb of blood alcohol concentration (BAC), which pattern increased during BAC plateau. Only baseline data (without alcohol intake) were used in the current study.	
Kamarajan et al, (2005)	59	29.4 (7.14)	53	13.46 (2.89)	Alcohol	30 participants were alcoholic patients according to SDM-5	Cannabis, cocaine, amphetamine, hallucinogens	100	50	No	No	Yes	No	5 (11.02)	297(20)	There was no difference between alcoholics and controls in commission error rate and go RT	

Kreusch et al, (2014)	30	21.47 (3.01)	47	14.5 (2.37)	Alcohol	15 heavy drinkers with AUDIT >11		100	25	No	No	No	No	4 (4.55)	335(61)	For the letter GNG task, heavy drinkers made more commission errors than light drinkers, while no difference on go RT.
Littel et al, (2012)	56	21.91 (4.17)	61	Missing	Game	25 excessive gamers had a Videogame Addiction Test (VAT) score>2.5	Cannabis, cocaine, amphetamine, ecstasy, hallucinogens	636	11.6	No	Yes	Yes	No	43 (19.08)	339(55)	Excessive gamers made more commission errors than controls.
López-Caneda et al, (2014)	57	18.74 (0.55)	46	14 (0)	Alcohol	Binge drinkers binge drink at least once a week OR binge drink once a month with at least three drinks per hour for at least two years.	Cannabis	150	50	No	No	Yes	No	4 (4.06)	529(40)	There was no difference between binge drinkers and controls in go RT and commission error rate.
Luijten et al, (2011)	78	21.46 (2.05)	72	14.44 (1.13)	Tobacco	Smokers smoked at least 10 cigarettes per day for at least two years.	Cannabis, cocaine, amphetamine, ecstasy, hallucinogens	896	25	Yes	No	No	No	30 (15.09)	261(32)	Smokers made more commission errors than controls, while there was no correlation between daily cigarette consumption and commission error rate. And there was no group difference of go RT.
Luijten, O'Connor et al, (2013)	32	25.25 (5.21)	63	15.75 (2.2)	Tobacco	Smokers smoked at least 15 cigarettes per day for at least two years.	Cannabis, cocaine, amphetamine, hallucinogens	160	12.5	No	No	Yes	No	21 (13.94)	408(53)	Smokers did not differ from controls in commission error rate and go RT.

Luijten, Veltman et al, (2013)	48	22.17 (2.42)	67	14.89 (1.45)	Tobacco	Smokers smoked at least 15 cigarettes per day for at least three years.	Cannabis, cocaine, amphetamine, ecstasy, hallucinogens	927	11.86	No	Yes	Yes	No	39 (14.49)	356(51)	Smokers made more commission errors and also had longer go RT compared with non-smokers
Luijten et al, (2015)	16	21.38 (3.03)	100	15.88 (1.02)	Gamer	Problem gamers scored more than 2.5 on VAT.	Cannabis, cocaine, amphetamine, ecstasy, hallucinogens	927	12	No	Yes	Yes	No	43 (14.96)	409(42)	Problem gamers made more commission errors than controls, while there was no group difference in go RT.
Mahmood et al, (2013)	36	18.64 (0.34)	72	14 (0)	No specific	High frequency substance users had any drug use over 180 occasions.	Cannabis, cocaine, amphetamine, ecstasy, hallucinogens	180	32	No	No	Yes	No	14 (8.82)		There was no difference in commission error rate between high and low-frequency substance users.
Petit et al, (2012)	35	21.29 (1.98)	51	14 (0)	Alcohol	Heavy social drinkers had on average 20 drinks per week, and with AUDIT>11.		798	30	Yes	No	No	No	19 (7.67)	288(31)	Heavy drinkers made more commission error than light drinkers when the background picture is alcohol-related.
Paz et al, (2018)[b*]	203	21.06 (1.87)	48	15.04 (1.1)	No specific	Binge drink was assessed with the last three items of alcohol use questionnaire (AUQ).	Cannabis, cocaine, ecstasy	256	12.5	No	No	No	No	14 (10.15)	393(45)	The correlation between the commission error rate and binge score was not reported.

Pike et al, (2015)[c]	91	39.93 (8.28)	64	11.67 (1.91)	Cocaine	There was no control group and all participants reported cocaine use for the past month.	Cannabis, amphetamine, hallucinogens	125	20	Yes	No	Yes	Yes	10 (12.13)	356(60)	Cocaine users made more commission errors to a no-go target following a cocaine image as the go cue compared to a neutral image as a go cue; While the correlation between severity of use and inhibition performance was not reported.
Quednow et al, (2007)	51	24.29 (4.75)	100	12.69 (1.46)	Ecstasy	Ecstasy group used ecstasy 50 times over a period of at least 1 year. Cannabis group was chronic users of cannabis.	Cannabis, cocaine, amphetamine, hallucinogens	160	50	No	Yes	Yes	No	25 (12.35)	1168(283)	Ecstasy group made more commission errors than cannabis users who performed as well as the controls. Besides, across groups, commission error rate correlated with cumulative cannabis dose, years of amphetamine use, cocaine use per week, years of cocaine use and the cumulative cocaine dose.
Rass et al, (2014)	82	25.29 (5.36)	48	15.82 (1.91)	Tobacco	Daily smokers smoked<25 cigarettes per day, daily use for at least 1 year, and scored ≥4 on the FTND.	Cannabis, cocaine, amphetamine	500	20	No	No	No	No	25 (12.25)	239(43)	Smokers and controls did not differ in commission error rate and go RT
Roberts et al, (2010)	39	22.38 (2.93)	51	16.44 (2.45)	Ecstasy & cannabis	Ecstasy group were current ecstasy users and consumed at least 40 ecstasy tablets over a period of a year.	cocaine, amphetamine	500	10	No	Yes	Yes	No	45 (17.51)	316(42)	Ecstasy users did not differ from controls in commission error rate and go RT.

Roberts et al, (2013)	59	23.26 (2.99)	44	Missing	Ecstasy & poly	Ecstasy group needs to take ecstasy for at least five occasions.	Cannabis, cocaine	240	25	No	No	Yes	No	6 (5.78)	363(61)	Ecstasy polysubstance users, non-ecstasy polysubstance users, and controls did not differ in commission error rate and go RT.
Rossiter et al, (2012)	124	26.43 (6.79)	48	15.47 (2.48)	Alcohol	The harmful alcohol use group had an AUDIT score no less than 16.		160	12.5	No	Yes	Yes	No	37 (17.25)	338(55)	Harmful alcohol use group made fewer commission errors compared with controls under the delayed reward condition; The opposite pattern was observed under the immediate punishment condition. And there was no difference with regards to go RT.
Takagi et al, (2011, 2014)	30	20.49 (1.48)	43	10.73 (1.51)	Inhalant & cannabis	Inhalant users had inhalants daily or almost daily use for more than 12 months.	cocaine, amphetamine, ecstasy	300	10	No	No	No	No	22 (15.8)	332(48)	[ref 2011] Inhalant users and controls did not differ in commission error rate and go RT; [ref 2014] The inhalant group had lower d-prime score compared with controls.
Verdejo-García et al, (2012)	19	28.68 (7.92)	58	12.26 (1.19)	Opiate	Opiate dependents had an average score on SDS (Severity of Dependence Scale) of 8.3.	Cannabis, cocaine, amphetamine, ecstasy, hallucinogens	300	23.33	No	No	No	No	17 (9.08)	315(36)	Controls made more commission errors compared with opiate dependents.
Wetherill et al, (2013)	18	19.49 (0.99)	33	12.89 (1.32)	Alcohol	Heavy drinkers at least had 4 drinks per occasion, less than once per month but more than once per year.	Cannabis	180	32	No	No	Yes	No	9 (6.79)	514(62)	Heavy drinkers and controls did not differ in commission error rate.

Note: go RT = correct go trials reaction time; M = mean; SD = standard deviation.

[*]Unpublished dataset at time of searching literature

Why comparison between substance users and controls could not be obtained from the original paper

[a] interested in the difference between the increasing and decreasing limb of BAC but we only used baseline data when participants were sober

[b] the correlation between commission error rate and binge score was not reported

[c] focused on the experimental effect (different kinds of cued GNG) instead of the individual difference

Table 2

Description of included SST studies (dependent variable is SSRT)

Study	Demographic information				substance of use			Task parameters					Dependent variables			
	Sample size (reserved)	Age M (SD)	Male %	Education years M (SD)	Main substance in the original paper	criteria for the heavy/problematic substance use group	Other substance use info provided	Trial number	No-go percentage %	Stop signal modality	SSD	SSRT computation	SSRT M (SD)	Go RT M (SD)	Main behavioral findings	Number of ca excluded (including th whole groups
Bidwell et al. (2013)[a]	150	21.56 (3.16)	64	Missing	Cannabis	All participants used marijuana at least once a week in the past month and at least 10 times in the past 6 months.		192	25	Auditory	Staircase	Other	274(66)	576(183)	There was no correlation between SSRT and BIS-11.	1
Bø et al. (2016)	119	21.71 (2.12)	5	14.95 (1.56)	Alcohol	All participants use alcohol on a regular basis, binge score was calculated based on the last three items of the Alcohol Use Questionnaire.		320	25	Auditory	Staircase	Other	189(54)	357(76)	Binge score was not a significant predictor of SSRT	2
Bø et al. (2017)*	186	36.22 (12.8)	32	16.45(2.7)	Depression	No special requirement for substance use	Cannabis, cocaine	320	25	Auditory	Staircase	Other	187(50)	413(123)	Weekly alcohol consumption negatively correlated with SSRT.	120
Colzato et al. (2007)	24	29.33	83	Missing	Cocaine	Recreational cocaine users should consume cocaine 1 to 4 gram per month by snorting route for a minimum of two years.		520	30	Visual	Staircase	Integration	215(27)	375(39)	SSRT was significantly longer for cocaine users than non-users.	
Courtney et al. (2012, 2013)[b]	304	37.15 (10.81)	7	13.29 (3.25)	Alcohol	All participants were problem drinkers, with a minimum of 48 standard drinks per month.		64	25	Auditory	Staircase	Other	241(90)	525(96)	Response inhibition (SSRT) could not explain alcohol use and alcohol problems.	6

de Ruiter et al. (2012)	35	34.2 (9.25)	1	11.86 (1.67)	Gambling & Tobacco	Problem gamblers were diagnosed by SDM-5. Heavy smokers smoked at least 15 cigarettes per day.		360	32	Visual	Staircase	Other	270(46)	435(87)	Problem gamblers, heavy smokers, and controls did not differ in SSRT and go RT	17
Filbey et al. (2013)	74	24.14 (7.2)	74	13.5(2.68)	Cannabis	All participants were cannabis users with at least 4 uses per week for at least 6 months prior. Among them, 44 were diagnosed with cannabis dependents according to SDM-5.	cocaine, ecstasy	384	25	Auditory	Staircase	Integration	190(44)	512(76)	Cannabis dependents and cannabis non-dependents did not differ in SSRT and go RT.	
Fillmore et al. (2002)	44	40.27 (6.66)	61	12.18(1.4)	Cocaine	Participants in the cocaine use group need to score ≥4 on the Drug and Abuse Screening Test (DAST), habitual cocaine use for a minimum of 6 month and past week cocaine use.		176	27	Auditory	Fixed	Integration	318(91)	Missing	Cocaine users showed prolonged SSRT compared with controls, while go RT was comparable.	
Galván et al. (2011)	59	19.49 (1.1)	61	13.75 (1.17)	Tobacco	Daily smokers should smoke daily for at least 6 months.		256	25	Auditory	Staircase	Integration	164(61)	479(90)	Smokers did not differ from controls in SSRT and go RT	74

Glass et al. (2009)	495	44.1 (4.97)	47	13.9(2.27)	Alcohol & Tobacco	A self-developed variable of alcohol severity was used, with 65 participants categorized as alcohol abuse, 55 as alcohol dependence without physical dependence, 33 as alcohol dependence with physical dependence.	Cannabis, cocaine	256	25	Auditory	Staircase	Other	250(76)	839(202)	Both SSRT and go RT had a significant negative correlation with alcoholism severity.	77
Karoly et al. (2014)[b]	53	28.3 (6.91)	47	15.55 (1.85)	Alcohol	All participants were categorized as heavy drinkers with at least two drinks (three for men) twice per week. Among them, twelve participants were with AUDIT score ≥16.	Cannabis	198	26	Auditory	Staircase	Integration	172(48)	568(108)	The relationship between SSRT/go RT and alcohol use was not reported in the paper.	
Kräplin et al. (2015)	75	26 (7.92)	39	11.74 (0.76)	Gambling & Tobacco	Pathological gambling (PG) and nicotine dependence (ND) were dragonized with DSM-5.	Cannabis	205	20	Visual	Staircase	Integration	298(93)	557(159)	PG lead to prolonged SSRT compared with controls. There is no difference between PG and ND; ND and PG comorbid ND with regard to SSRT.	44

Moallem et al. (2012)	287	30.97 (10.61)	73	14.68 (2.59)	Alcohol & Tobacco	Smokers should smoke cigarettes no less than 10 per day and had less than 3 months' smoking abstinence in the past year. Heavy drinkers were defined by National Institute on Alcohol Abuse and Alcoholism (NIAAA), i.e. drinks per week >14 (women > 7) or drinks per occasion ≥ 5 (≥ 4 for women) at least once per month over the past year.		64	25	Auditory	Staircase	Other	223(88)	509(90)	Heavy drinkers, smokers, heavy drink smokers did not differ in SSRT and go RT; After controlling for age, heavy drinker smokers showed slower go RT compared with smokers.	11
Papachristou et al. (2012a)[c]	42	25.5 (9.66)	24	Missing	Alcohol	All participants were light to moderate social drinkers with an average AUDIT score of 7.7.		256	25	Auditory	Staircase	Other	222(50)	344(63)	The relationship between AUDIT and SSRT was not reported.	
Papachristou et al. (2012b)	75	23.29 (5.2)	33	Missing	Alcohol	Heavy and light social drinkers were classified by the cut-off score of 11 of AUDIT.		256	25	Auditory	Staircase	Other	203(32)	Missing	Light and heavy drinkers had similar SSRT.	
Paz et al. (2018)[de]	182	21.15 (1.83)	49	15.1(1.08)	Not specific	Binge drink was assessed with the last three items of alcohol use questionnaire (AUQ).	Cannabis, cocaine, ecstasy	256	25	Auditory	Staircase	Integration	227(47)	694(175)	The relationship between SSRT and binge score was not reported.	21
Tsaur et al. (2015)[e]	21	34.73 (12.47)	76	13.9(1.18)	Tobacco	All participants were smokers with at least 10 cigarettes per day for the past year.		192	25	Auditory	Staircase	Other	252(52)	560(112)	Only baseline data was used. The correlation between daily cigarette smoking and SSRT was not reported.	

Vonmoos et al. (2013)	163	30.03 (8.18)	71	10.45 (1.74)	Cocaine	Cocaine dependence was diagnosed with DSM-IV. All cocaine users should have cocaine as the primary used illegal drug, cocaine use of >0.5 g per month, and abstinence duration of <6 months.	Cannabis, ecstasy, amphetamine	192	25	Auditory	Staircase	Integration	291(63)	745(192)	Two cocaine use group (recreational users and dependent users) and the control group had similar SSRT and go RT.	3
Zack et al. (2015)	12	33.75 (11.23)	1	15.92 (0.52)	Gambling	Pathological gambling (PG) was diagnosed with SDM-5 and a score ≥5 on the SOGS (South Oaks Gambling Screen).	Cannabis	512	25	Auditory	Staircase	Other	182(27)	482(115)	There was no difference between PG and healthy controls with regard to go RT and SSRT.	13

Note: DV: dependent variable; SSD = stop-signal delay; SSRT = stop-signal reaction time; go RT = correct go trials reaction time; M = mean; SD = standard deviation.

[*]Unpublished dataset at time of searching literature

Why comparison between substance users and controls could not be obtained from the original paper

[a] did regression analysis

[b] only reported MRI results

[c] focused on experimental effect rather than individual difference with a within-subject design

[d] the correlation between commission error rate and binge score was not reported

[e] longitudinal study along substance abstinence, only baseline data were used

Table 3a

Quality assessment scores of included GNG studies according to the NHLBI Quality Assessment Tool

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality Rating
Ames et al, (2014)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Claus et al, (2013)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Hendershot et al, (2015)	yes	yes	NR	yes	no	yes	yes	yes	yes	yes	yes	NR	NA	yes	**fair**
Kamarajan et al, (2005)	yes	yes	NR	no	no	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Kreusch et al, (2014)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Littel et al, (2012)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
López-Caneda et al, (2014)	yes	yes	NR	yes	no	yes	yes	yes	yes	yes	yes	NR	NA	yes	**good**
Luijten et al, (2011)	yes	yes	NR	yes	no	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Luijten, O'Connor et al, (2013)	yes	no	NR	CD	yes	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Luijten, Veltman et al, (2013)	yes	yes	NR	CD	no	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Luijten et al, (2015)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Mahmood et al, (2013)	yes	yes	NR	yes	no	yes	yes	yes	yes	yes	yes	NR	NA	yes	**good**
Petit et al, (2012)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Paz et al, (2018)	yes	yes	NR	yes	no	yes	yes	yes	yes	yes	yes	NR	NA	no	**fair**
Pike et al, (2015)	yes	yes	NR	yes	yes	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Quednow et al, (2007)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Rass et al, (2014)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Roberts et al, (2010)	yes	no	NR	yes	no	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Roberts et al, (2013)	yes	no	NR	yes	no	no	no	no	yes	no	yes	NR	NA	yes	**suboptimal**
Rossiter et al, (2012)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Takagi et al, (2011)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Takagi et al, (2014)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	no	**fair**
Verdejo-García et al, (2012)	yes	yes	NR	yes	yes	yes	yes	yes	yes	no	yes	NR	NA	yes	**good**
Wetherill et al, (2013)	yes	yes	NR	yes	no	yes	yes	no	yes	no	yes	NR	yes	yes	**good**

Note: CD: cannot determine; NA: not applicable; NR: not reported; Meanings of criteria Q1-Q14 can be found in Table S2.

Table 3b

Quality assessment scores of included SST studies according to the NHLBI Quality Assessment Tool

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality Rating
Bidwell et al. (2013)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Bø et al. (2016)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Bø et al. (2017)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Colzato et al. (2007)	yes	yes	NR	yes	no	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Courtney et al. (2012)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Courtney et al. (2013)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
de Ruiter et al. (2012)	yes	yes	NR	no	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Filbey et al. (2013)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Fillmore et al. (2002)	yes	yes	NR	yes	no	no	no	no	yes	no	yes	yes	NA	yes	**fair**
Galván et al. (2011)	yes	yes	NR	yes	no	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Glass et al. (2009)	yes	no	NR	no	no	yes	yes	yes	yes	no	yes	yes	NA	yes	**good**
Karoly et al. (2014)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	no	**fair**
Kräplin et al. (2015)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Moallem et al. (2012)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Papachristou et al. (2012a)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Papachristou et al. (2012b)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Paz et al, (2018)	yes	yes	NR	yes	no	yes	yes	yes	yes	yes	yes	NR	NA	no	**fair**
Tsaur et al. (2015)	yes	yes	NR	yes	yes	no	CD	yes	yes	no	yes	NR	yes	yes	**fair**
Vonmoos et al. (2013)	yes	yes	NR	yes	yes	yes	CD	yes	yes	no	yes	NR	NA	yes	**good**
Zack et al. (2015)	yes	yes	NR	yes	yes	no	no	no	yes	no	yes	NR	NA	yes	**fair**

Note: CD: cannot determine; NA: not applicable; NR: not reported; Meanings of criteria Q1-Q14 can be found in Table S2.

Content of Supplemental Information

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Figures

Figure S1: P-curve on the significant association between substance use and response inhibition.

Figure S2a: Histograms of demographics and continuous variables of substance use in GNG: commission error rate

Figure S2b: Pie charts of discrete variables of substance use in GNG: commission error rate

Figure S2c: Pie charts of task parameters in GNG: commission error rate

Figure S3a: Histograms of demographics and continuous variables of substance use in SST: SSRT

Figure S3b: Pie charts of discrete variables of substance use in SST: SSRT

Figure S3c: Pie charts of task parameters in SST: SSRT

Other

S1: Demographics and task parameters (detailed instruction and discussion)

S2: Analyses of the effect of study type (behavioral/EEG/fMRI)

S3: Optional variables list

S4: Analyses of speed-accuracy trade-off in GNG

S5: Analyses of the effect of 'number of substances used' in the model

S6: Effect of interactions 'alcohol×demographics' and 'alcohol×task parameters'

S7: List of studies that provided raw data but were not included (plus reasons)

S8: Results on go RT in GNG task and SST

S9: Effect size comparison between studies included and those not included (plus **Fig. S4**)

References

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Table S1a

Essential variables (GNG)

Subject No.	demographic variables			substance use		GNG variables (Report at least one measure) Percentage of no-go signals:_____		
	Age (years)	Sex (F/M)	Education (highest level)	Alcohol	Tobacco	No-Go Commission Errors	Go Omission Errors	Go RT
1								
2								
3								
4								
5								
……								

Note:

1. Check the unit of demographic variables, *if different from suggestion please provide additive legend or explanation*
2. *For the use of alcohol and tobacco, please provide the measurement you used (e.g. the unit, Does the number signifies the average amount per day during how many past weeks/months?)*

Table S1b

Essential variables (SST)

Subject No.	demographic variables			substance use		SST (Report at least one measure) Percentage of stop signals:_____	
	Age (years)	Sex (F/M)	Education (highest level)	Alcohol	Tobacco	SSRT	Go RT
1							
2							
3							
4							
……							

Note:

1. Check the unit of demographic variables, *if different from suggestion please provide additive legend or explanation*
2. *For the use of alcohol and tobacco, please provide the measurement you used (e.g. the unit, the number signifies the average amount per day during the past several weeks?)*

Table S2

Quality assessment tool for observational cohort and cross-sectional studies (National Heart, Lung, and Blood Institute (NHLBI), 2014)

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Note: CD, cannot determine; NA, not applicable; NR, not reported

Table S3: P-curve disclosure table: association between substance use and response inhibition

original paper	1) quoted text from original paper indicating prediction of interests to researchers	2) study design	3) key statistical result	4) quoted test from the original paper with statistical results	5) results	6) robustness results
Ames et al. (2014)	We expect that alcohol cues as No-Go signals will lead to more inhibitory errors (i.e., difficulty withholding a response). Thus, these errors should be greater among heavier drinkers relative to the lighter drinkers.	two-cell: heavy drinker vs light drinker	difference of means	Although not statistically significant, heavy drinkers made more inhibitory errors during the No-Go trials than the lighter drinkers ($p < 0.106$).	$t(39)=1.26$, $p=0.21$ (calculated from mean, SE and N in table)	
Bidwell et al. (2013)	We also examined the interactions among cannabinoid-related genetic variation and two measures of behavioral impulsivity: (a) the capacity to inhibit already initiated responses as measured by the Stop Signal Task (Logan et al., 1997) (no clear hypothesis on behavioral measures)	NA (focused on gene: CNR1 or FAAH)	NA	NA	NA	
Bø & Landrø, (2017)	We expect to find a stair-case relation between a greater level of alcohol consumption and SSRT and PES, respectively. The highest consumers are expected to have longer SSRTs, indicative of less efficient inhibition	one way ANCOVA, 5-cell: compare five drinking levels on SSRT.	linear trend/main effect	There was a significant main effect of alcohol consumption on SSRT at the $p < .05$ level for five consumption levels [$F(4, 389) = 2.867$, $p = .023$, $\mu = .029$].	$F(4,389)=2.867$, $p=0.023$	

Note: NA: not available

Filbey & Yezhuvath, (2013)	We expected greater functional connectivity between inhibitory control networks in cannabis-dependent users vs. nondependent cannabis users.	two-cell: cannabis dependent vs nondependent	difference of means	The groups also did not differ in … or SSRT (dependent: 185.1 ±30 ms, nondependent: 198.4 ±38.2 ms).	t(72)=1.67, p=0.10	
Fillmore et al. (2002)	We predicted that cocaine abusing individuals would display a specific deficit in the ability to inhibit behavioral prepotent responses as measured in the stop-signal paradigm.	two-cell: controls vs cocaine users	difference of means	Table 2 also shows that cocaine users displayed significantly longer SSRTs than did controls (t42=2.4, P=0.020). A 2 group ANCOVA also obtained a significant difference in SSRT after controlling for subjects' weekly alcohol use, (F1,41=7.4, P=0.009).	t(42)=2.4, p=0.02	
Galván et al. (2011)	Task-related activity in PFC regions, critical for response inhibition, would be negatively associated with smoking behavior.	two-cell: smokers vs nonsmokers	difference of means	There were no significant group differences in task performance	t(48)=0.7342, p=0.466 (calculated from mean and SD in table)	
Glass et al. (2009)	We examined whether chronic alcoholism and chronic smoking have effects on executive function	regression: alcohol severity & smoking in predicting executive function	correlation coefficients	read from table: alcohol severity: r(238) = -0.167; smoking: r(238) = -0.221	1) r(238)=-0.167, p= 0.009; 2) r(238)=-0.221, p < 0.001	
Kamarajan et al. (2005)	In the present study, along with ERPs, we have therefore attempted to examine the spatial distribution of current source density (CSD) which may give distinct topographic features specific to alcoholism during response inhibition. (no clear hypothesis about the direction)	two-cell: alcoholic vs. control	difference of means	Although alcoholics committed more errors during the button-press responses of Go and No-Go condition separately, this difference was not statistically significant.	t(59)= 1.605, p= 0.114	

Karoly et al. (2014)	Further explicate the nature of the relationship between cue-induced craving and response inhibition among heavy drinkers with a stop-signal paradigm that is combined with the presentation of visual alcohol cues and control (nonalcoholic beverage) cues. (no clear hypothesis is stated)	NA (focused on fMRI)	NA	NA	NA	
Kräplin et al. (2015)	1)We hypothesized that the comorbid PG (pathological gambling, without ND: nicotine dependence) group would show higher response and choice impulsivity than healthy controls; 2)Therefore, our hypothesis was that PG (without ND) is related to an increased choice impulsivity compared to ND (nicotine dependence), whereas response impulsivity may be comparable to ND; 3)We hypothesized an additive effect of comorbid PG and ND on impulsivity compared with only ND.	a couple of two-cell: control vs PG, PG vs ND, PG vs PG&ND	difference of means	The PG group displayed a significant higher SSRT than the control group (ATT/average treatment effect of the treated = 75.67, 95% confidence interval, CI [1.84, 206.12]),	NA	
Kreusch et al. (2014)	We first hypothesized that heavy drinkers, by comparison to light drinkers, would exhibit inhibition deficits revealed by more FA during No-go trials involving letters; in the modified Go/No-go task, we expected reduced inhibition performances towards alcohol-related cues in heavy drinkers as compared to light drinkers.	1) two-cell (light drinker vs heavy drinker); 2) 2 (heavy vs light drinker)×2(high vs. low alcohol avoider)× (alcohol-related picture vs. neutral picture)	1) difference of means; 2) no clear hypothesis on this, no further report on this three-way interaction	The t-tests computed … and the percentage of FAs in the letter Go/No-go task revealed a significant difference on FAs (t(28)= 2.24, p= 0.03). Heavy drinkers made more FA than light drinkers (mean= 5.6%, SD=5.4 in heavy drinkers and mean= 2.1%, SD = 2.5 in light drinkers).	t(28)=2.24, p=0.03	

Note: NA: not available

Littel et al. (2012)	We hypothesize excessive gamers to show reduced NoGo N2 amplitudes in response to NoGo trials and reduced ERN and Pe amplitudes in response to errors. Because of inconsistencies in results of previous studies, no specific hypotheses are formulated with regard to behavioral indices of response inhibition.	2 (group: control vs excessive computer gamers) × (trial: go vs no-go)	simple effect (only the effect of group on no-go trials)	Furthermore, a significant Group × Error interaction was found, $F(1,50) = 11.44$, $P < 0.001$. Excessive gamers made more errors in response to No-Go trials (54%, $M = 40.12$, $SD = 11.93$) than controls (41%,$M = 30.67$, $SD = 12.17$; $P < 0.01$).	$t(50)=2.82$, $p=0.007$ (self-calculated from mean and SD)	
López-Caneda et al (2014)	We tested the hypotheses that …lower amplitudes of the NoGo-P3 component in Ex-BDs than in BDs but larger than in controls. no hypothesis about behavioral data.	3-cell (control vs. binge drinkers vs. ex-binge drinkers)	linear trend	There were no significant differences between groups (Controls, BDs, and Ex-BDs) for any of the behavioral variables analyzed (RT, percentage of correct responses, and percentage of correct inhibitions).	$F(2,54)=0.42$, $p=0.66$	
Luijten et al. (2011)	It is expected that smokers will make more mistakes when they have to inhibit their response to infrequent NoGo stimuli; we expect these effects to be more pronounced on trials which include smoking-related stimuli.	2 (group: smokers vs. non-smokers) ×2 (picture: smoking vs. non-smoking) (attenuated interaction)	two-way interaction	Trend to significance was found for the Group × Inhibition interaction, $F(1,37) = 3.27$, $p =0.08$.	$F(1,37)=3.27$, $p=0.08$	

Luijten, O'Connor et al. (2013)	We hypothesized that smokers would have significantly greater difficulty inhibiting their response to an immediate rewarding stimulus when compared to matched control participants, neutral conditions or both. With regard to punishment, we expected that non-smoking controls would adopt a more cautious responding style when failed inhibition resulted in an immediate punishment, while this was not expected to influence behavior to the same extent in smokers.	Reward: 2 (group: smokers vs. controls) ×2 (condition: neutral vs. reward) Punishment: 2 (group: smokers vs. controls) ×2 (condition: neutral vs. punishment)	Reward: two simple effects Punishment: two simple effects	For both reward & punishment: RM-ANOVAs did not show significant main or interaction effects of group and condition for either NoGo, Go and Go-Money accuracy rates.	Calculate from the table in paper: neutral condition, control vs smoker: $t(34)=0.42$, $p=0.70$; reward condition, control vs smoker: $t(34)=0.10$, $p=0.92$; punishment condition, control vs smoker: $t(34)=1.40$, $p=0.17$	
Luijten, Veltman et al. (2013)	We hypothesized that haloperidol will reduce inhibitory control and associated brain activation. Second, based on the inverted 'U' curve theory of dopamine and cognitive control, and reported baseline differences between smokers and controls in dopamine D2 receptor density in subcortical regions, we expected that haloperidol will have differential effects on brain activation associated with inhibitory control in smokers and non-smokers. (no hypothesis about behavioral data)	2 (medication: haloperidol vs placebo) ×2(group: smokers vs. controls)× 2 (trial: go vs no-go)	only one simple effect, under the placebo condition, smokers vs controls.	We performed an additional explorative Group x Condition RM-ANOVA for accuracy rates on the first test occasion in order to exclude possible learning effects on task performance. A Group x Task Condition interaction was found, $F(1,46)=4.72$, $p<0.05$. Post-hoc t-tests revealed that, for NoGo trials, smokers performed less accurately than non-smoking controls ($p<0.05$; $M_{smokers}=53.31$, $SD=14.22$, $M_{controls}=61.90$, $SD=15.10$), whereas there was no difference for Go accuracy between the groups, $F(1,46)=0.33$,ns.	$t(46)=2.03$, $p=0.048$ (self-calculated from mean and SD)	

Luijten et al. (2015)	Impairments in inhibitory control, error processing, and attentional control were expected for behavioral measures of the Go/No-Go and the Stroop task.	2 (go vs. no-go)×2 (problem gamers vs. controls)	simple effect	In addition, both the Group main effect, showing reduced accuracy in problem gamers, $F(1,31)=4,91$, $p<0.05$, and the Group×Inhibition interaction, $F(1,31)=4,27$, $p < 0.05$,were significant. Post-hoc tests revealed that problem gamers were less accurate for No-Go trials, $p<0.05$, compared with non-problematic gamers,	$t(32)=2.177$, $p= 0.037$ (self-calculated from M and SD value)	
Moallem & Ray (2012)	This study compares across substance using groups to examine unique and additive effects of impulsivity. (no clear hypothesis other than this was reported)	3-cell: controls vs smokers vs heavy drinker smokers	linear trend	Initial omnibus tests revealed no significant main effect of group on SSRT ($F(2, 376)=1.42$, $p=.24$)	$F(2,376)=1.42$, $p=0.24$	
Papachristou et al. (2012)	It is expected that heavy drinkers will score higher on measures of trait impulsivity and STR and will display poorer response inhibition relative to light drinkers.	2 (drinking group: heavy vs. light drinkers)×2 (impulsivity: high vs. low in impulsivity)×4 (cue exposure: baseline water, water exposure, baseline alcohol, alcohol exposure)	difference between means	There was no significant difference in the SST ($F[1, 40]<1$, n.s.) and CARROT ($F[1, 40]<1$, n.s.) performances between the two drinking groups.	$t(40)=0.10$, $p=0.92$ (self-calculated from mean and SD in table)	
Papachristou et al. (2012)	It is hypothesized that social drinkers with impaired response inhibition experience higher cue-elicited craving for alcohol than social drinkers with good response inhibition	correlation between AUDIT score and SSRT (this is not the main analysis in the paper but our focus)	correlation coefficient	$r(36) = -0.17$ (from the table)	$r(36)=-0.17$, $p=0.31$	

Paz et al. (2018)	We first hypothesized that increases in binge drinking behavior throughout participation will be significantly correlated with poor inhibitory performance assessed at follow-up (T2). Second, we hypothesized those who substantially increased their binge drinking during participation, compared to those who substantially decreased their binge drinking, will show a decline in inhibitory performance from baseline assessment (T1) to T2.	1) correlation (negative between the increase in binge score and inhibition). However, this was done separately for males and females; 2) 2 (group: increase binge score vs decrease binge score) × (session: T1 vs T2) (reversing interaction)	1) correlation coefficient; 2) two simple effect	1) A significant correlation was found with a change in AUQ binge score and SSRT among females only, where an increase in binge drinking score from T1 to T2 positively correlated with poor performance in the SST at T2, $r(82) = 0.276$, $p = 0.012$. 2) Results of the repeated-measures ANOVA showed no significant main or interaction effects between binge drinking groups and inhibitory performance from T1 to T2 (see Table 5).	NA	
Quednow et al. (2007)	We expected elevated levels of impulsivity and a decision-making deficit in MDMA users in comparison with both control groups.	3-cell: (MDMA vs. cannabis vs. control)	MDMA vs control	An initial ANOVA did not reveal any significant main effect between the groups in the dependent variables	calculated through mean and SD displayed in the table, MDMA vs control: $t(31)=0.32$, $p=0.75$	cannabis vs control: $t(30)=1.00$, $p=0.32$

Note: NA: not available

Rass et al. (2014)	Although not statistically significant, heavy drinkers made more inhibitory errors during the NoGo trials than the lighter drinkers ($p < 0.106$). We expected that smokers would commit more commission errors (false positives) and exhibit faster reaction times (RTs) than ITS (intermittent smokers) and nonsmokers during inhibitory control tasks, reflecting greater behavioral disinhibition. We expected that it would fall between smokers and nonsmokers in terms of those measures.	3 (smoker vs ITS vs control) × 2 (condition: frequent vs rare)	under the rare condition, smoker vs control	For the assessment of errors, a group (3) ×condition (2) repeated measures ANOVA found more errors in the rare condition ($F[1,79] = 231.66$, $p < 0.001$). There was no main effect of group ($F[2,79] = .08$) and no group _ condition interaction ($F[2,79] = .51$).	t(50)=0.96, p=0.34 (calculated from provided data)	under the rare condition, smoker vs ITS: t(50)=1.69, p=0.96
Roberts et al. (2010)	The hypothesis was that polysubstance users who predominantly used ecstasy would report elevated measures of state and trait impulsivity and reveal dysregulated brain functioning during response inhibition and performance monitoring compared to healthy controls.	two-cell (group: ecstasy vs control)	difference of means	Independent-group t-tests revealed that the groups did not differ … on any GO/NOGO performance measures including % STOPs ($p \leq 0.5$), the error of commission reaction times ($p \leq 0.6$) …	t(38)=1.769, p=0.085 (calculated from mean, SE and N from table)	

Roberts et al. (2013)	The aim of the current study was to observe whether there are any behavioral or electrophysiological differences between ecstasy users and controls in a task measuring inhibitory control (Go/No-Go). In view of the previous literature it is predicted that any behavioral differences will be negligible, however observable differences in components of the elicited ERPs are predicted in line with compensatory mechanisms.	3-cell: (ecstasy users vs polydrug users vs control)	linear trend	Univariate ANOVA revealed that there was no significant difference between groups in performance on this task $F(2,57)=1.15$, $p=0.33$. The mean 'No-Go' errors (i.e. responding to a letter other than an X that required no response/inhibition of response) were used as the measure of performance in this case (Ecstasy users: 2.7±1.95, polydrug users: 3.4±2.80, drug naïve: 4.35±4.92).	$F(2,57)=1.15$, $p=0.32$	
Rossiter et al. (2012)	The aim of these contingencies was (1) to examine the influence of delayed reward on inhibitory control over immediate reward-related stimuli (when compared to non-reward stimuli), in the presence or absence of punishment; and (2) the influence of alcohol abuse behavior on the interaction between reward, punishment and inhibitory control. (no clear hypothesis is declared)	2 (group: harmful drinkers vs non-hazardous drinkers) ×2 (gender: male vs. female) × 3(condition: neutral vs delayed reward vs immediate punishment)	only on simple effect: under neutral condition, the group effect	A 2 group × 2 gender × 3 incentive condition (Neutral, DR, IP) ANOVA, indicated response inhibition performance was significantly influenced by incentive context, $F(2,162) = 22.6$, $p = .00$, but not group, $F(1,81) = .01$, $p = .90$, or gender, $F(1,81) = .13$, $p = .71$.	$t(83)=0.63$, $p=0.53$ (self-calculated from mean, se and N in table)	

Takagi et al. (2014)	We hypothesized the inhalant users would have lower d-prime scores relative to the other groups.	3-cell: (inhalant vs cannabis vs control)	difference between means: inhalant vs control; inhalant vs cannabis	There were significant differences between the three groups on measures of d-prime on the Go/No-Go task. Games–Howell post hoc tests revealed significant differences between the inhalant and control groups (p = .021, d = .88), with inhalant users having significantly lower d_ scores. The d-prime score between the inhalant and cannabis groups was not significant (p = .21, d = .55). but we focused on commission error rate	calculated from the data provided: inhalant users vs controls: t(47)=2.49, p= 0.17; inhalant users vs cannabis users: NA	
Tsaur et al. (2015)	We hypothesized that craving would be intensified and response inhibition deteriorated during abstinence compared with baseline.	NA (we only used baseline data, not compare baseline with abstinence periods)	NA	NA	NA	
Verdejo-García et al. (2012)	We sought to address these unresolved questions by examining the performance of opiate dependent individuals on a series of well-validated measures of attention and inhibitory control both before and after exposure to an autobiographical craving script (looks like exploratory analysis)	two-cell (opiate-dependent vs. control) (this is what we are interested)	difference of means	There were no significant differences in performance on tests of attention and inhibitory control between groups (p> 0.05), with the exception of GNG number of commission errors, which was significantly higher in controls, t=−2.81, p=0.007.	t(56)=−2.81, p=0.007	

Note: NA: not available

Vonmoosa et al. (2013)	We expected to find increased trait and behavioral impulsivity in DCU and similar, albeit less pronounced, results in RCU	3-cell (control vs recreational cocaine users vs dependent cocaine users)	linear trend	None of the SST parameters revealed a significant main group effect.	F(2,153)=1.885, p=0.16	
Zack. et al (2015)	It was predicted that AMPH would lead to increased cardiovascular and HPA response in PG vs HC subjects, as indexed by HR, blood pressure and plasma cortisol response, particularly in the later stages of the dose.	MANOVA controls vs. pathological gamblers on different outputs of SST	difference of means	A MANOVA of Go RT, SSRT, go errors and stop errors on the Stop Signal Task yielded no significant effects, ps>0.13. SSRT, 185 (31) ms for HC vs 220 (86) ms for PG;	t(21)=1.27, p=0.22	

Table S4a

The full model results and percentage of missing values per variable: GNG commission error

Variables	Missing data %	β	t	p	95% Confidence Interval	
					Lower Bound	Upper Bound
Age	0.0%	-0.01	-2.52	0.01*	-0.03	0.00
Sex	0.0%	0.00	0.01	0.99	-0.02	0.02
Education years	11.3%	-0.01	-1.87	0.06	-0.02	0.00
Alc_Q	0.0%	0.00	-0.04	0.97	-0.04	0.04
Cig_Q	8.8%	0.00	-0.61	0.54	-0.02	0.01
cannabis_lifetime	29.7%	0.00	-0.14	0.89	-0.01	0.01
cocaine_lifetime	34.8%	-0.01	-0.58	0.56	-0.03	0.01
ampetamine_lifetime	57.5%	0.00	-0.25	0.80	-0.03	0.02
XTC_lifetime	57.9%	0.00	-0.22	0.83	-0.02	0.01
hallusinogens_lifetime	68.0%	0.00	0.43	0.67	-0.01	0.02
working_memory	0.0%	0.11	5.31	0.00**	0.07	0.15
substance_related	0.0%	0.01	0.71	0.48	-0.01	0.03
task_complexity	0.0%	-0.01	-0.30	0.76	-0.04	0.03
cue_GNG	0.0%	-0.03	-1.03	0.30	-0.08	0.02
nogo_percentage	0.0%	-0.05	-3.14	0.00**	-0.07	-0.02
trial_number	0.0%	0.03	2.17	0.03*	0.00	0.06
Alc*cig	9.2%	-0.01	-1.52	0.13	-0.03	0.00
Alc*can	27.2%	-0.01	-0.69	0.49	-0.03	0.01
Alc*cocaine	30.1%	0.00	0.27	0.79	-0.02	0.03
Alc*amphe	58.1%	0.00	0.03	0.97	-0.03	0.04
Alc*XTC	57.9%	0.00	0.14	0.89	-0.02	0.03
Alc*HALL	68.2%	-0.01	-0.69	0.49	-0.04	0.02
Cig*can	35.3%	0.01	1.01	0.31	-0.01	0.02
Cig*cocaine	40.4%	0.00	-0.56	0.58	-0.02	0.01
Cig*XTC	63.6%	0.00	-0.32	0.75	-0.01	0.01
Can*cocaine	34.9%	0.00	0.34	0.73	-0.01	0.02
Can*amphe	57.8%	0.00	-0.01	0.99	-0.01	0.01
Can*XTC	58.0%	-0.01	-0.64	0.52	-0.02	0.01
Coc*amphe	57.9%	0.00	-0.32	0.75	-0.02	0.01
Coc*XTC	58.1%	0.00	-0.48	0.63	-0.02	0.01
Coc*HALL	68.0%	0.00	-0.14	0.89	-0.02	0.02
Amphe*HALL	68.0%	0.00	-0.68	0.50	-0.02	0.01
Alc*sex	0.0%	-0.01	-0.77	0.44	-0.05	0.02
Cig*sex	8.8%	0.00	-0.19	0.85	-0.01	0.01
Can*sex	29.7%	0.00	-0.12	0.91	-0.01	0.01
Coc*sex	34.8%	0.01	0.86	0.39	-0.01	0.03
Amphe*sex	57.5%	0.00	0.39	0.70	-0.01	0.02
XTC*sex	57.9%	0.00	-0.39	0.69	-0.02	0.01
HALL*sex	68.0%	-0.01	-0.71	0.48	-0.02	0.01
Alc*cig*sex	9.2%	0.01	0.73	0.47	-0.01	0.02
Alc*can*sex	30.1%	0.01	1.46	0.14	0.00	0.03
Alc*cocaine*sex	35.1%	0.00	-0.07	0.94	-0.02	0.02
Alc*amphe*sex	58.1%	-0.01	-0.36	0.72	-0.04	0.03
Alc*XTC*sex	57.9%	0.01	0.82	0.41	-0.01	0.04
Alc*HALL*sex	68.2%	0.00	-0.30	0.76	-0.03	0.03
Cig*can*sex	35.3%	0.00	-0.44	0.66	-0.01	0.01
Cig*cocaine*sex	40.4%	0.01	1.31	0.19	0.00	0.02
Cig*XTC*sex	63.6%	-0.01	-1.07	0.28	-0.02	0.01
Can*cocaine*sex	34.9%	0.00	-0.52	0.60	-0.02	0.01
Can*XTC*sex	58.0%	0.00	0.54	0.59	-0.01	0.02
Co*amphe*sex	57.9%	0.00	0.00	1.00	-0.01	0.01

*Note: *p<0.05, **p<0.01*

Table S4b

The full model results and percentage of missing values per variable: GNG go RT

Variables	Missing value%	β	t	p	95% Confidence Interval	
					Lower Bound	Upper Bound
Age	0.0%	11.21	3.48	0.00**	4.90	17.52
Sex	0.0%	-2.33	-0.47	0.64	-12.05	7.38
Education_years	10.9%	-0.74	-0.27	0.78	-6.04	4.56
Alc_Q	0.0%	-3.35	-0.35	0.73	-22.35	15.65
Cig_Q	13.6%	0.41	0.11	0.91	-6.59	7.41
cannabis_lifetime	30.2%	3.69	0.91	0.36	-4.28	11.65
cocaine_lifetime	35.5%	-2.73	-0.51	0.61	-13.26	7.81
ampetamine_lifetime	59.0%	3.39	0.59	0.56	-7.91	14.70
XTC_lifetime	59.2%	-1.27	-0.31	0.76	-9.29	6.74
hallusinogens_lifetime	69.4%	4.40	0.94	0.35	-4.84	13.63
working_memory	0.0%	126.53	2.82	0.00**	38.55	214.51
substance_related	0.0%	5.33	0.86	0.39	-6.77	17.42
task_complexity	0.0%	-15.44	-0.40	0.69	-90.50	59.61
cue_GNG	0.0%	-23.54	-0.43	0.67	-130.63	83.56
nogo_percentage	0.0%	102.02	3.18	0.00**	39.14	164.90
trial_number	0.0%	-60.57	-1.77	0.08†	-127.56	6.43
Alc*cig	14.0%	-2.09	-0.48	0.63	-10.70	6.51
Alc*can	30.6%	3.37	0.67	0.50	-6.51	13.25
Alc*cocaine	35.7%	5.07	0.77	0.44	-7.82	17.95
Alc*amphe	59.3%	-1.08	-0.12	0.91	-19.28	17.12
Alc*XTC	59.2%	-5.37	-0.75	0.45	-19.48	8.75
Alc*HALL	69.6%	5.27	0.69	0.49	-9.82	20.36
Cig*can	39.0%	2.24	0.69	0.49	-4.14	8.63
Cig*cocaine	44.2%	1.41	0.45	0.65	-4.68	7.50
Cig*XTC	68.1%	1.22	0.40	0.69	-4.72	7.16
Can*cocaine	35.5%	-3.78	-0.86	0.39	-12.45	4.89
Can*amphe	59.0%	7.61	1.56	0.12	-1.99	17.21
Can*XTC	59.3%	1.72	0.44	0.66	-5.91	9.36
Coc*amphe	59.2%	-4.02	-0.88	0.38	-13.01	4.97
Coc*XTC	59.4%	1.13	0.27	0.79	-7.02	9.28
Coc*HALL	69.4%	-5.31	-1.07	0.28	-15.04	4.42
Amphe*HALL	69.4%	4.70	1.11	0.27	-3.63	13.02
Alc*sex	0.0%	-5.29	-0.54	0.59	-24.48	13.90
Cig*sex	13.6%	0.26	0.08	0.94	-6.14	6.65
Can*sex	30.2%	1.18	0.32	0.75	-5.97	8.33
Coc*sex	35.5%	-7.37	-1.32	0.19	-18.34	3.61
Amphe*sex	59.0%	-2.13	-0.42	0.67	-12.06	7.80
XTC*sex	59.2%	-1.48	-0.37	0.71	-9.28	6.32
HALL*sex	69.4%	7.38	1.43	0.15	-2.78	17.53
Alc*cig*sex	14.0%	-1.85	-0.41	0.68	-10.72	7.02
Alc*can*sex	30.6%	2.19	0.44	0.66	-7.66	12.03
Alc*cocaine*sex	35.7%	2.10	0.33	0.74	-10.32	14.51
Alc*amphe*sex	59.3%	-3.41	-0.37	0.71	-21.57	14.75
Alc*XTC*sex	59.2%	-1.32	-0.18	0.85	-15.45	12.81
Alc*HALL*sex	69.6%	-2.63	-0.34	0.73	-17.70	12.44
Cig*can*sex	39.0%	1.19	0.40	0.69	-4.66	7.03
Cig*cocaine*sex	44.2%	3.12	0.99	0.32	-3.07	9.31
Cig*XTC*sex	68.1%	-0.43	-0.14	0.89	-6.30	5.45
Can*cocaine*sex	35.5%	-2.27	-0.50	0.62	-11.13	6.59
Can*XTC*sex	59.3%	3.73	1.07	0.29	-3.13	10.58
Coc*amphe*sex	59.2%	-2.77	-0.65	0.52	-11.17	5.63

*Note: †0.05*p<0.05, **p<0.01*

Table S4c

The full model results and percentage of missing values per variable: SST SSRT

Variables	Missing value%	β	t	p	95% Confidence Interval	
					Lower Bound	Upper Bound
sex	3.40%	-3.81	-1.19	0.23	-10.09	2.47
age	0.00%	12.95	5.92	0.00**	8.66	17.24
education_years	14.20%	-9.7	-5.15	0.00**	-13.39	-6.01
alc_Q	5.40%	-0.57	-0.18	0.86	-6.84	5.7
cig_Q	5.40%	2.15	0.89	0.38	-2.61	6.92
cannabis_lifetime	44.30%	6.21	1.41	0.16	-2.44	14.86
cocaine_lifetime	51.30%	3.41	0.7	0.48	-6.13	12.95
XTC_lifetime	82.50%	-1.9	-0.81	0.42	-6.53	2.73
SST_version	0.00%	-27.16	-2.06	0.04*	-53.02	-1.3
SSD	0.00%	-39.51	-2.19	0.03*	-74.92	-4.1
SSRT_computation	0.00%	-3.82	-0.47	0.64	-19.62	11.98
trial_number	0.00%	-17.49	-2.38	0.02*	-31.92	-3.07
nogo_percentage	0.00%	-6.56	-1.07	0.29	-18.63	5.52
Alc*cig	8.60%	2.6	1.05	0.3	-2.28	7.48
Alc*cannabis	48.30%	-4.56	-0.85	0.39	-15.08	5.96
Alc*cocaine	53.60%	9.75	1.88	0.06†	-0.46	19.96
Alc*MDMA	82.50%	-0.3	-0.1	0.92	-6.32	5.72
Alc*sex	7.10%	-1.25	-0.43	0.67	-7.02	4.51
Cig*cannabis	49.10%	-1.91	-0.75	0.45	-6.9	3.09
Cig*cocaine	55.10%	-5.05	-1.73	0.08†	-10.8	0.69
Cig*MDMA	83.20%	0.81	0.4	0.69	-3.22	4.85
Cig*sex	7.10%	0.3	0.13	0.9	-4.26	4.85
Can*sex	47.20%	3.02	0.74	0.46	-4.96	11
Can*cocaine	56.40%	3.76	1.03	0.3	-3.4	10.91
Coc*sex	54.30%	-4.74	-1.29	0.2	-12	2.52
Cocaine*XTC	82.50%	-0.51	-0.23	0.81	-4.83	3.8
XTC*sex	83.40%	-0.64	-0.34	0.73	-4.33	3.05
Alc*cig*sex	10.30%	-0.72	-0.29	0.77	-5.65	4.22
Alc*cannabis*sex	49.60%	-0.12	-0.02	0.98	-12.22	11.97
Alc*cocaine*sex	55.00%	-1.94	-0.39	0.7	-11.84	7.96
Alc*XTC*sex	83.40%	-0.87	-0.31	0.76	-6.46	4.72
Cig*cannabis*sex	50.50%	-4.58	-1.76	0.08†	-9.72	0.55
Cig*cocaine*sex	56.50%	-0.81	-0.27	0.78	-6.63	5.01
Cig*XTC*sex	84.00%	-0.42	-0.22	0.83	-4.21	3.38
Can*cocaine*sex	59.30%	6.66	1.93	0.05*	-0.13	13.45
Cocaine*XTC*sex	83.40%	-0.69	-0.34	0.74	-4.73	3.35

*Note: $^{\dagger}0.05<p<0.1$, *$p<0.05$, **$p<0.01$*

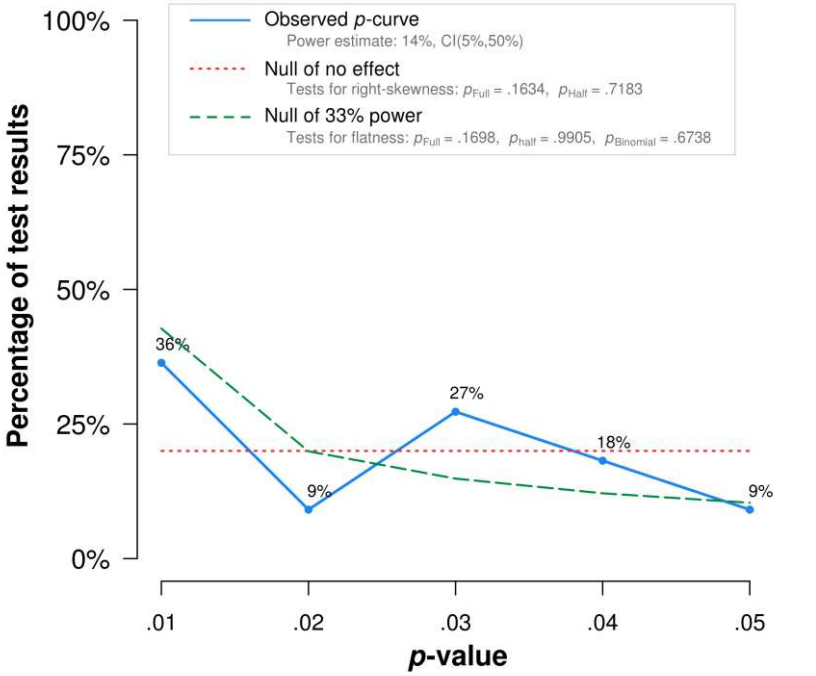
Table S4d

The full model results and percentage of missing values per variable: SST go RT

Variables	Missing value%	β	t	p	95% Confidence Interval	
					Lower Bound	Upper Bound
age	0.00%	32.55	6.96	0.00**	23.39	41.71
sex	3.6%	-2.05	-0.35	0.73	-13.58	9.47
education_years	11.5%	-14.11	-3.54	0.00**	-21.91	-6.30
alc_Q	5.7%	-3.12	-0.30	0.76	-23.31	17.07
cig_Q	5.7%	-2.10	-0.42	0.68	-11.99	7.79
cannabis_lifetime	41.5%	2.14	0.29	0.77	-12.34	16.63
cocaine_lifetime	50.6%	-0.95	-0.12	0.91	-16.96	15.07
XTC_lifetime	81.6%	0.44	0.10	0.92	-8.25	9.12
SSRT_comput	0.00%	48.25	1.47	0.14	-16.15	112.65
SST_version	0.00%	41.99	0.91	0.36	-48.47	132.45
nogo_percentage	0.00%	-4.33	-0.21	0.84	-45.15	36.49
trial_number	0.00%	-31.25	-1.06	0.29	-89.14	26.64
Alc*cig	9.0%	0.44	0.10	0.92	-8.68	9.57
Alc*cannabis	45.7%	1.39	0.13	0.90	-20.27	23.04
Alc*cocaine	53.0%	2.59	0.19	0.85	-24.76	29.93
Alc*sex	7.5%	1.05	0.10	0.92	-18.79	20.89
Alc*XTC	81.6%	-1.18	-0.20	0.84	-12.72	10.36
Cig*cannabis	46.6%	1.74	0.40	0.69	-6.87	10.35
Cig*cocaine	54.6%	-9.50	-1.92	0.06†	-19.22	0.21
Cig*sex	7.5%	4.20	0.87	0.38	-5.27	13.66
Cig*XTC	82.2%	0.83	0.19	0.85	-7.64	9.30
Can*cocaine	54.1%	-3.80	-0.63	0.53	-15.68	8.07
Can*sex	44.5%	-1.46	-0.21	0.83	-15.03	12.12
Coc*sex	53.8%	2.14	0.30	0.76	-11.69	15.96
Cocaine*XTC	81.6%	2.23	0.49	0.63	-6.73	11.20
MDMA*sex	82.5%	-0.60	-0.14	0.89	-8.90	7.69
Alc*cig*sex	10.9%	3.04	0.68	0.49	-5.69	11.78
Alc*cannabis*sex	47.1%	5.36	0.48	0.63	-16.46	27.19
Alc*cocaine*sex	54.5%	6.04	0.41	0.68	-22.70	34.79
Alc*XTC*sex	82.5%	0.70	0.12	0.91	-11.27	12.67
Cig*cannabis*sex	48.0%	-0.47	-0.10	0.92	-9.37	8.44
Cig*cocaine*sex	56.1%	0.87	0.17	0.87	-9.30	11.04
Cig*XTC*sex	83.2%	-1.45	-0.35	0.72	-9.52	6.62
Can*cocaine*sex	57.1%	-6.08	-1.04	0.30	-17.57	5.42
Cocaine*XTC*sex	82.5%	-2.89	-0.68	0.50	-11.31	5.52

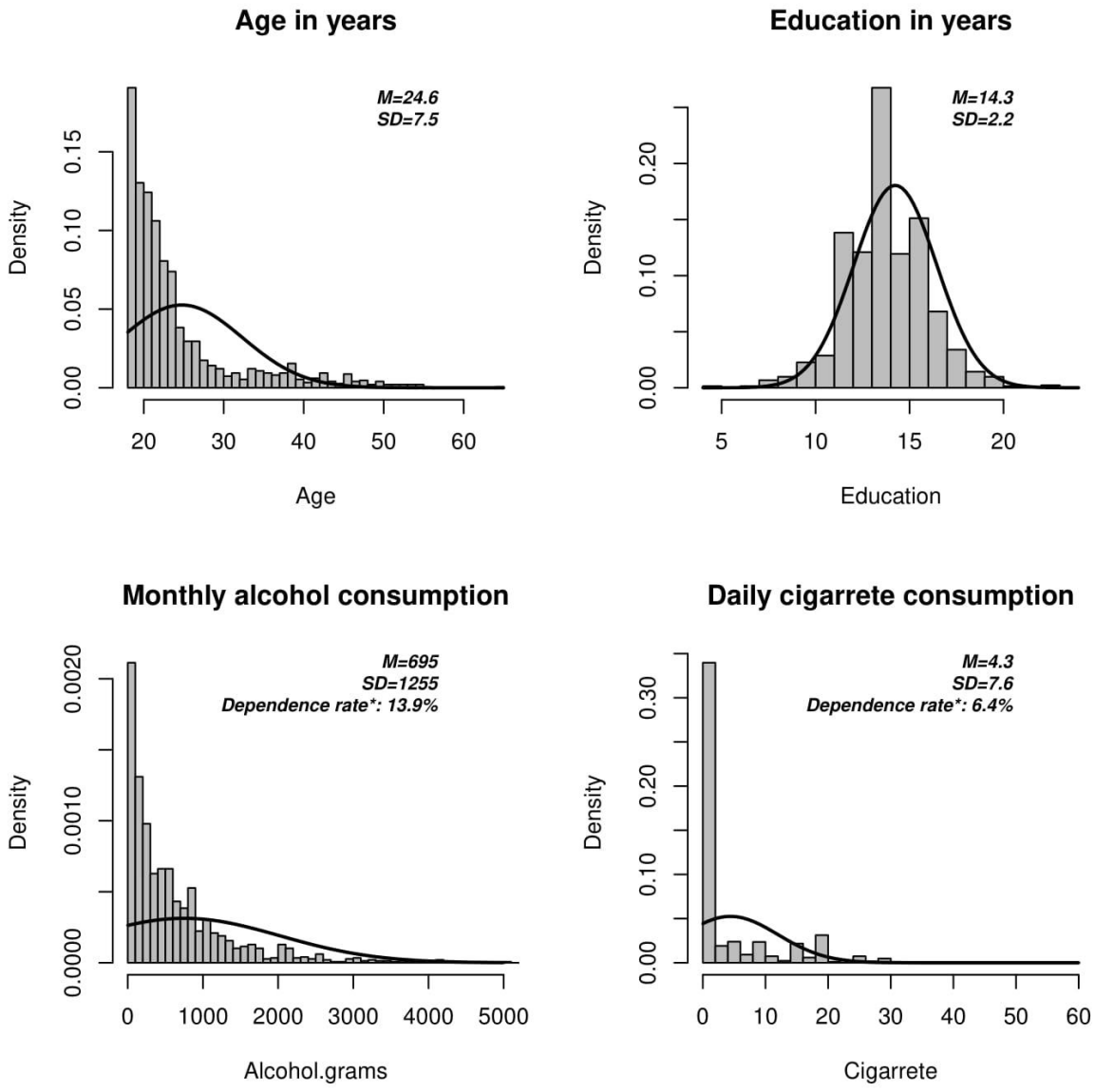
*Note: †0.05<p<0.1, *p<0.05*

Figure S1: P-curve on the significant association between substance use and response inhibition.



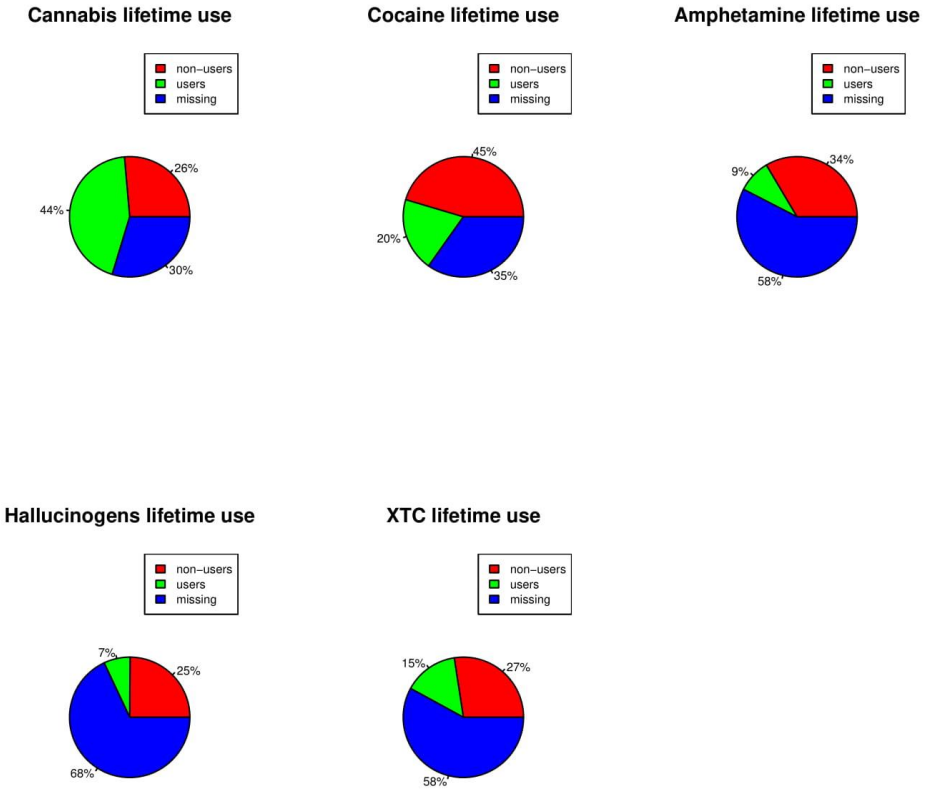
Note: The observed *p*-curve includes 11 statistically significant ($p < .05$) results, of which 8 are $p < .025$.
There were 20 additional results entered but excluded from *p*-curve because they were $p > .05$.

Figure S2a: Histograms of demographics and continuous variables of substance use in GNG: commission error rate



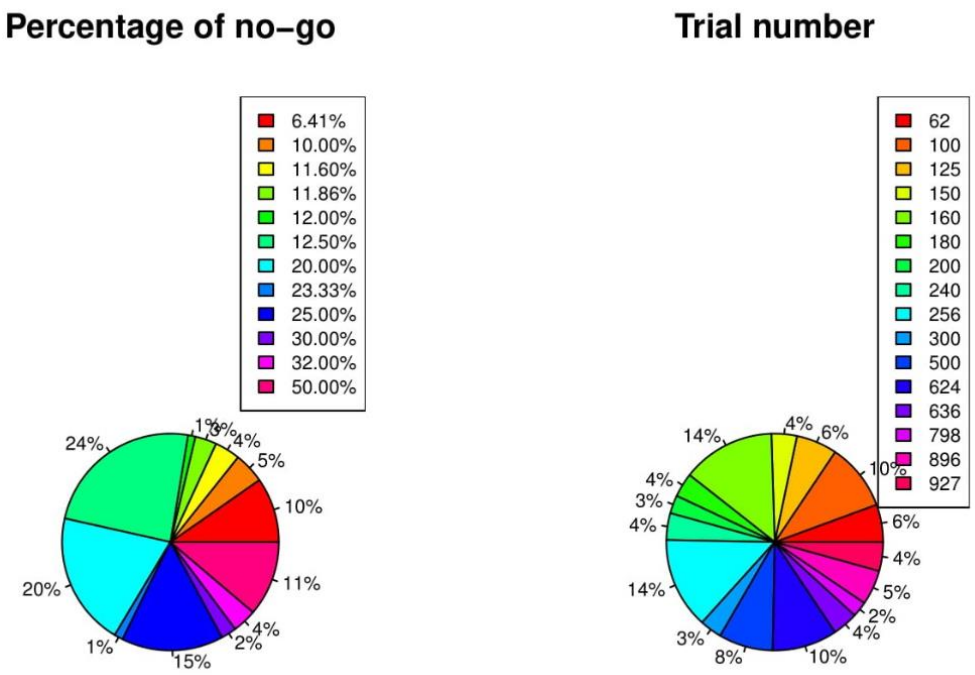
**Alcohol dependence was roughly evaluated through DSM-IV, alcoholics reported in the original paper or an AUDIT (Alcohol Use Disorders Identification Test) score higher than 16; Tobacco dependence was roughly evaluated if FTND (Fagerstrom Test for Nicotine Dependence) was above 5. This plot is based on raw data provided before imputation.*

Figure S2b: Pie charts of discrete variables of substance use in GNG: commission error rate



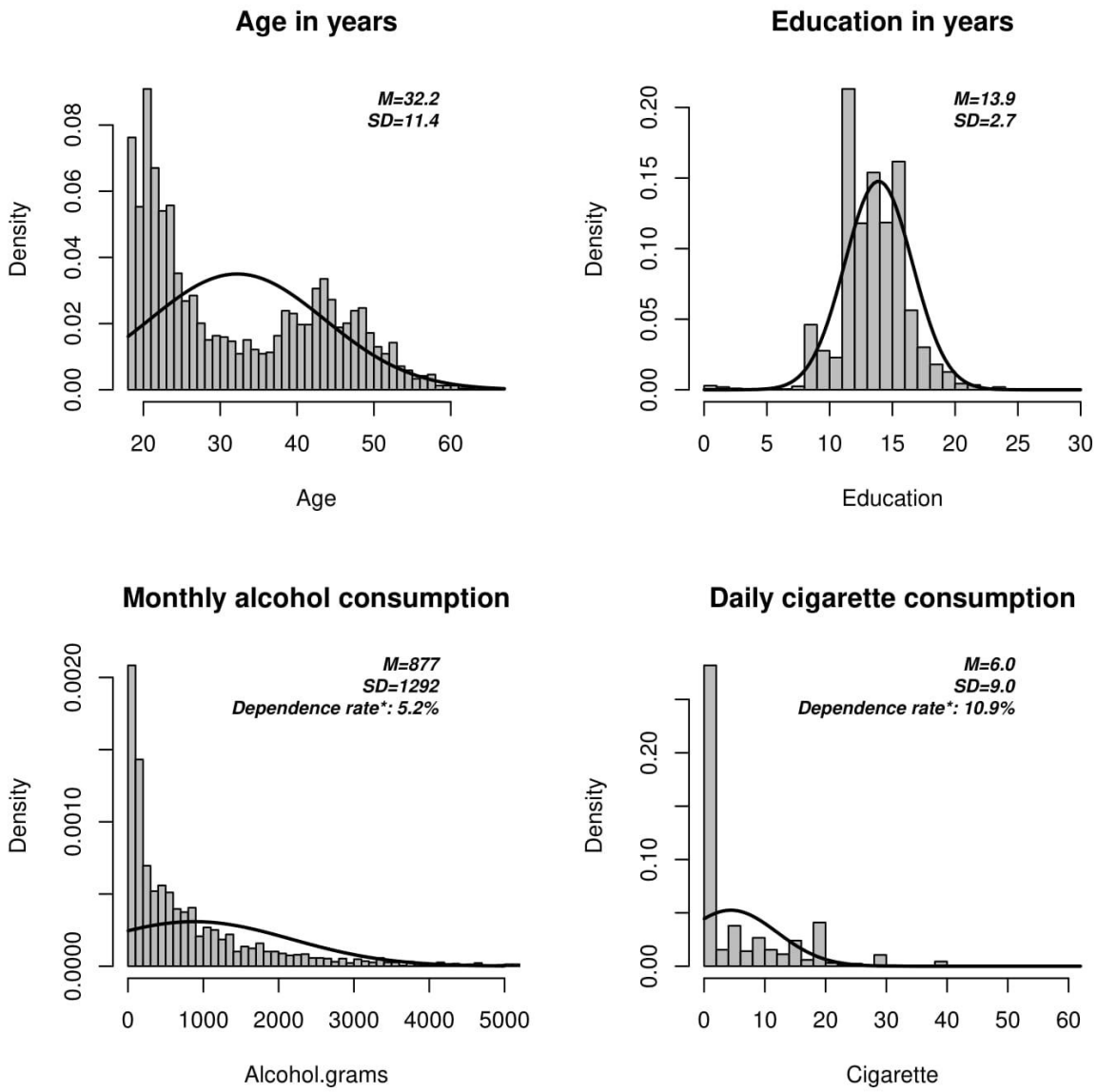
*****_This plot is based on raw data provided before imputation._

Figure S2c: Pie charts of task parameters in GNG: commission error rate



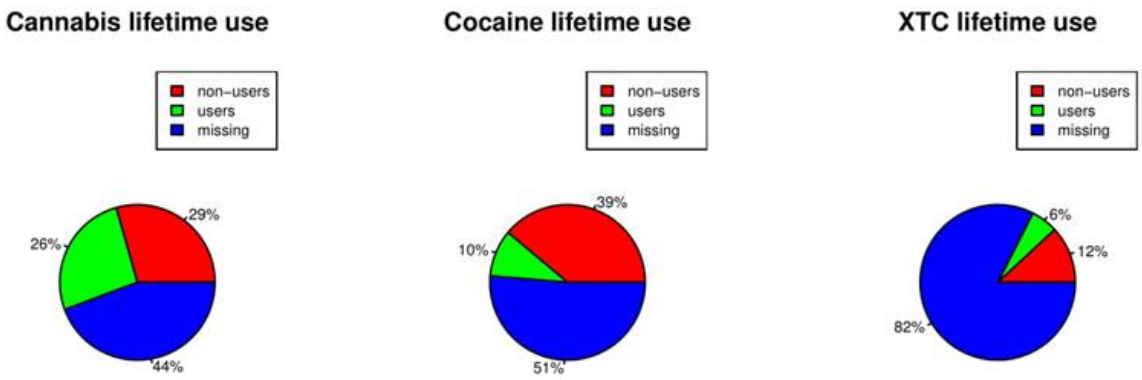
*****_This plot is based on raw data provided before imputation, and there was no missing data._

Figure S3a: Histograms of demographics and continuous variables of substance use in SST: SSRT



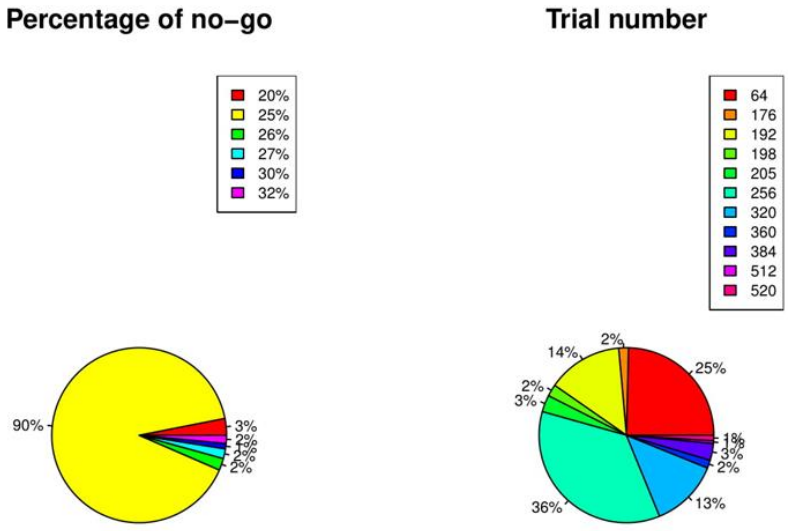
**Alcohol dependence was roughly evaluated if the AUDIT (Alcohol Use Disorders Identification Test) score was higher than 16; Tobacco dependence was roughly evaluated if FTND (Fagerstrom Test for Nicotine Dependence) was above 5. This plot is based on raw data provided before imputation.*

Figure S3b: Pie charts of discrete variables of substance use in SST: SSRT



** This plot is based on raw data provided before imputation.*

Figure S3c: Pie charts of task parameters in SST: SSRT



** This plot is based on raw data provided before imputation, and there was no missing data.*

S1: Demographics and task parameters (detailed Introduction and Discussion)

Introduction

Sex

For a single study, it is hard to investigate the effect of sex due to the often disproportionate ratio of male and female substance users. For instance, out of the 62 studies in Stavro and colleagues' meta-analysis on alcoholism and cognitive deficits, 40% sampled only males, 19% assessed both males and females at a comparable rate and 5% studied female-only samples (Stavro, Pelletier, & Potvin, 2013).

Sex may, however, relate to response inhibition. Research about sex differences in response inhibition produced mixed results (Weafer & de Wit, 2014). Some found females outperformed males (Sjoberg & Cole, 2018). Some other studies reported no sex difference in behavioral outcomes (i.e. SSRT) but show differential brain activation (e.g., globus pallidus, thalamus, bilateral medial frontal cortex and cingulate cortex, and parahippocampal gyrus) related to response inhibition (Li, Huang, Constable, & Sinha, 2006; White et al., 2014).

Furthermore, sex may moderate the association between substance use and inhibition (Fattore & Melis, 2016). Taking alcohol studies as an example, the effect of alcohol on inhibition was reported to be most pronounced in females (Nederkoorn, Baltus, Guerrieri, & Wiers, 2009; Smith, Iredale, & Mattick, 2016; Smith & Mattick, 2013). However, other studies reported no main effect of sex nor interactions between sex and substance use on response inhibition (Henges & Marczinski, 2012; López-Caneda et al., 2012; Rossiter, Thompson, & Hester, 2012; van der Plas, Crone, van den Wildenberg, Tranel, & Bechara, 2009). In the current study, therefore, we included main and moderating effects of sex on the relationship between substance use and response inhibition.

Age & education years

A second demographic variable that should be controlled for is age, as inhibition performance typically shows an inverted U-shaped curve across the lifespan (Williams, Ponesse, Schachar, Logan, & Tannock, 1999), with a peak during young adulthood. As the studies in our mega-analysis only include adults, we included age as a continuous linear variable. In addition, education level also has a substantial effect on inhibitory performance, with middle to highly educated participants performing better (e.g., Stroop Color and Word Test, van Hooren et al., 2007). Therefore, education level was also taken into account in the present study.

GNG task characteristics

In order to aggregate data over studies, we should account for six task characteristics that may affect inhibition and differ between studies. First, no-go percentages in the GNG task vary largely between studies. There is a debate about whether inhibition is required in equiprobable GNG tasks, where responding and non-responding is required to an equal extent (Aron, Robbins, & Poldrack, 2014; Wessel, 2018). In line with Smith and colleagues (2014), we included these studies into our analysis while controlling for no-go percentage. Second, the number of trials differed a lot between studies, ranging from 40 to 600 in Metin and colleagues' meta-analysis on ADHD (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012). The number of trials, however, could negatively impact the reliability of the outcome if there are too few, and induce fatigue effects if there are too many. Third, tasks also vary in working memory load. Working memory is taxed when the go and no-go signals are conditional. For instance, Luijten and colleagues (2015) required participants to press a button in response to letters (go trials) but to inhibit if the same letter was repeated (no-go trials). Here, the letter shown on the last trial should be stored in memory and updated continuously. Therefore, the main effect of working memory load of the task was considered. Fourth, studies also differed in whether the task context was substance-related or not. The GNG used in addiction research sometimes contains substance-related stimuli that are response-related (e.g., issue a response to non-alcohol-related pictures and inhibit responses to alcohol-related stimuli, Ames et al., 2014) or task-irrelevant (e.g., background consisting of smoking-related pictures and non-smoking-related pictures, Luijten, Littel, & Franken, 2011). According to the incentive sensitization theory of addiction, brain reward systems are hypersensitive to drugs and drug-associated stimuli (Robinson & Berridge, 1993, 2003). Consequently, the global response inhibition deficits in substance abusers would be especially pronounced when confronted with substance-associated stimuli (Zack et al., 2011). The main effect of this task characteristic rather than its interaction with substance was taken into account as incentive sensitization has been related to addiction in general and there are too few studies included to break it up for different substances (see Method). Fifth, GNG may include a cue predicting a go or no-go stimulus. Here, the urgency of inhibition is increased if the cue incorrectly predicts a go stimulus (Hendershot et al., 2015). Therefore, we took into account whether the task was cued or not. Finally, the level of task complexity also varied among studies with variations of stimulus-response (S-R) mappings. A design with only one go stimulus and one no-go stimulus is fairly easy, but it is harder if two or more stimuli are associated with either a

go or an inhibition instruction. The main effect of this task characteristic was therefore included.

SST characteristics

Similarly, five task characteristics that varied between SST studies might affect task performance. These include the number of experimental trials, stop-trial percentage, stop-signal delay settings, stop-signal modality, and SSRT calculation method. First, the number of trials used in the SST is highly inconsistent across studies, ranging from 96 to 1920 (review: Alderson, Rapport, & Kofler, 2007). This broad range obscured interpretations concerning the origin of performance differences, i.e., whether they reflected deficient response inhibition, an inability to sustain attention or both (Alderson et al., 2007). Second, stop signal probability varied between studies, which may affect go RT (Lansbergen, Böcker, Bekker, & Kenemans, 2007). Third, stop-signal modality varied. Studies traditionally use either visual go stimuli (e.g., "X" and "O") coupled with an auditory tone as the stop signal, or visual go and stop signal stimuli (Rubia, Oosterlaan, Sergeant, Brandeis, & Leeuwen, 1998). Auditory stop signals compared to visual stop signals shortened the stopping latency, as stop tones are perceived as more intense than visual stop signs (van der Schoot, Licht, Horsley, & Sergeant, 2005). Fourth, stop-signal delay (SSD, the interval between the onset of the go signal and the onset of the stop signal) varied. Basically, there are two procedures for determining the SSD. The fixed method uses a variety of fixed delays whereas the staircase tracking procedure adjusts the SSD as a function of inhibition success (Levitt, 1971). With fixed SSDs, participants are likely to delay their go response in anticipation of a stop signal (Logan, Schachar, & Tannock, 1997). In addition, although these two procedures evoked similar neural activities for successful inhibition, individual differences were more pronounced for fixed SSD (Fauth-Bühler et al., 2012). Fifth, SSRT calculation varied. Several methods for estimating SSRT are described in the literature (Logan, 1994), with the integration method currently considered the most reliable procedure (Verbruggen & Logan, 2009). We, therefore, controlled for these five variables by including them as main effects in the analysis.

Discussion

In addition to the analyses of the primary (substance) predictors, the current mega-analysis also found relationships between inhibition variables and demographics. First, age showed opposite effects in the two tasks, indicating better inhibition in the GNG with age and poorer inhibition in the SST. Although this may at first be surprising, it points to the

fundamentally different processes assessed with these two tasks: action restraint with the GNG and action cancellation with the SST. In the GNG, this age-related increase in accuracy is most likely due to the strategic slowing of responses, which was confirmed by longer go RTs we found. In the SST, older people need a longer time to cancel their initiated action, in line with previous findings (Keilp, Sackeim, & Mann, 2005). In addition, higher educated people demonstrated better inhibition in both tasks. An indirect reason is that high education level is related with the high intellectual ability (Deary, Penke, & Johnson, 2010), which is related to strong inhibitory control (Macapagal, Janssen, Fridberg, Finn, & Heiman, 2011). In terms of sex, no main effect nor interaction with substance use was significant. This is in line with the broader picture of rather weak sex differences in executive functions such as cognitive control (van der Plas et al., 2009), with exceptions for mental rotation (Garavan, Hester, Murphy, Fassbender, & Kelly, 2006) and fine motor tasks (Nicholson & Kimura, 1996). The absence of an interaction effect seems to contrast with the findings that females are more susceptible to the effects of substance use (Nederkoorn et al., 2009; Smith et al., 2016; Smith & Mattick, 2013). Yet, these studies mainly focused on alcohol use, studies considered multiple substances by sex interactions was rarely documented. Factors such as age (adolescents vs. young adults), the severity of use (with/without a diagnosis of SUD), abstinence that might moderate the substance by sex interaction can be considered in the future (Fattore & Melis, 2016).

In GNG, increased working memory demands resulted in more commission errors (Simmonds, Pekar, & Mostofsky, 2008), which is a likely result of a larger number of S-R associations that have to be kept in working memory. Our results also showed that the higher the no-go percentage, the lower the commission error rates: when the stop probability is low, there is strong readiness to give a response, which makes it difficult to stop (Donkers & van Boxtel, 2004). In addition, the number of experimental trials also played a role, with more trials inducing higher commission error rates, likely due to task-related fatigue. In addition, a somewhat surprising finding was that a modified substance-related task did not differ in results from the typical tasks using neutral stimuli. This would be in line with a recent meta-analysis, which showed that when publication bias was corrected, exposure to alcohol-related cues did not significantly impair response inhibition among alcohol users (Jones, Duckworth, Kersbergen, Clarke, & Field, 2018). However, note that in the current study only 5 out of 23 studies included used a substance-related version, and therefore power was low. In the SST, visual stop signals induced longer SSRT compared to auditory stop signals (in line with

Ramautar, Kok, & Ridderinkhof, 2006). One explanation is that the neural pathway for sound perception is shorter than that for visual perception (Elliott, 1968; Goldstone, 1968; Woodworth & Schlosberg, 1954). Alternatively, stop tones are perceived as more intense than visual stop signals (van der Schoot et al., 2005). In addition, in contrast to GNG findings, in the SST a larger number of trials led to shorter SSRTs. Practice effects might play a role, given that previous research has indicated that practicing SST indeed improved performance (Manuel, Bernasconi, & Spierer, 2013). Furthermore, compared to the staircase-tracking procedure, fixed SSDs resulted in longer SSRT. Based on direct comparisons, the tracking procedure is recommended (Verbruggen & Logan, 2009).

S2: Analyses of the effect of study type (behavioral/EEG/fMRI)

We performed two extra analyses to make sure study type (behavioral/EEG/fMRI) did not systematically influence behavioral performance (i.e., SSRT and commission rate).

In the first extra analysis, we added the variable 'research type' as a fixed effect in the original full model, followed by 100 imputations of missing values, then backward elimination based on *p*-values. This analysis procedure is exactly the same as what we have reported in the main analysis.

For the GNG commission error rates, in the initial full model with 52 variables, the effect of 'research type' was not significant (β = 0.01, p = 0.69, 95% CI [-0.050, 0.07]). In the stepwise elimination, it was removed from the model at the 9nd step (β = 0.01, p = 0.70, 95% CI [-0.05, 0.07]).

For SSRT, in the initial full model with 37 variables, the effect of 'research type' was not significant (β = -16.80, p = 0.11, 95% CI [-37.27, 3.58]). During stepwise elimination, it was removed from the model at the 22nd step (β = -17.87, p = 0.08, 95% CI [-37.82, 2.09]).

S3: Optional variables list

Demographic Variables:

☐ Country where study took place ☐ Race/Ethnicity

☐ Education (the highest level, if student sample please signify)

☐ Beck Depression Inventory ☐ State Trait Anxiety Inventory (trait/ state)

☐ Special populations involved? (e.g., ADHD, ODD/CD, Drug-dependent, intellectually challenged)

☐ other information collected, please explain

Alcohol:

☐ age of onset: ☐ years of use ☐ AUDIT score ☐ SADQ score

☐ Binge drinking score ☐ DSM-IV or DSM IIIR score on alcohol

☐ Craving for alcohol(Alcohol Urge Questionnaire)

☐ other information collected, please explain

Tobacco:

☐ age of onset

☐ Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)

☐ Subscales of Shiffman/JavikWithdrawal Scale

☐ Fagerström Test for Nicotine Dependence(FTND)

☐ other information collected, please explain

Cannabis

☐ Cannabis Use Disorder Identification Test - Revised (CUDIT-R)

☐ daily use of cannabis

☐ other information collected, please explain

Other drug use

☐ MDMA ☐ Opioids ☐ Methamphetamine

☐ Khat ☐ Amphetamine ☐ Hallucinogens ☐ Barbiturates

☐ Marijuana ☐ Cocaine

☐ other information collected, please explain

S4: Analyses of speed-accuracy trade-off in GNG

Speed-accuracy trade-off is a potential problem in GNG. In fact, in addition to analyzing commission error rates and go RT in GNG separately, we also analyzed their combined score. A balanced integration score (BIS) was calculated by subtracting the standardized go RT from the standardized correct response proportions according to Liesefeld and Janczyk (2019), a higher score thus indicating better performance. Similar analysis procedures as those reported in the main text were applied to BIS. Predictors in the final model included education years (β = 0.05, p = 0.04, 95% CI [0.003, 0.09]), no-go percentage (β = -0.40, p = 0.02, 95% CI [-0.56, -0.23]), and working memory load (β = -1.1, p < 0.01, 95% CI [-1.32, -0.88]). This indicated that higher educated people had better performance, lower no-go percentage induced better performance, and without working memory load produced better performance. All directions are as expected.

S5: Analyses of the effect of 'number of substances used' in the model

According to Kaag and colleagues (2017), a sum score of the number of substances used was calculated based on the imputed data. Then a multilevel regression analysis was conducted with predictors of demographics, task parameters, this sum score and its interaction with sex. In GNG, similarly, number of substance of use was not a predictor of commission error rates (β = -0.002, p = 0.68, 95% CI [-0.01, 0.01]), nor was its interaction with sex (β = -0.001, p = 0.83, 95% CI [-0.01, 0.01]). In the SST, this variable did not significantly predict SSRT (β = 3.63, p = 0.08, 95% CI [-0.48, 7.74]) nor did its interaction with sex (β = -0.91, p = 0.60, 95% CI [-4.32, 2.50]).

S6: Effect of interactions 'alcohol×demographics' & 'alcohol×task parameters'

We performed an extra analysis to explore the possible moderation effect of demographics and task parameters in the relationship between substance use and inhibition. As alcohol use was the most complete substance-related variable, as a first step, we tested its interactions with demographics (e.g., alcohol×age) and task parameters (e.g., alcohol×no-go percentage) for both tasks. The analysis procedure was similar to that of the main analysis.

We found that none of these interaction variables survived the stepwise elimination.

In the GNG commission error rate, predictors remained in the final model included working memory (β = 0.10, p < 0.01, 95% CI [0.07, 0.13]), age (β = -0.02, p < 0.01, 95% CI [-0.03, -

0.01]), no-go percentage (β = -0.04, p < 0.01, 95% CI [-0.07, -0.02]), trial number (β = 0.04, p = 0.002, 95% CI [0.02, 0.07]), alcohol×age (β = 0.01, p = 0.02, 95% CI [0.001, 0.02]) and alcohol (β = -0.005, p = 0.30, 95% CI [-0.01, 0.004]). Post-hoc test revealed that for light drinkers, older people made less commission errors (β = -0.02, t = -2.56, p = 0.01). This relationship was absent among heavy drinkers (β = -0.01, t = -1.50, p = 0.14). In addition, the effect of alcohol use was not significant either within the younger subsample (β = 0.003, t = 0.64, p = 0.52) nor within the older subsample (β = -0.002, t = -0.20, p = 0.84).

In the SST/SSRT, predictors reserved in the final model were age (β = 13.61, p < 0.01, 95% CI [9.45, 17.77]), education years (β = -9.64, p < 0.01, 95% CI [-13.24, -6.04]), cannabis (β = 6.52, p = 0.01, 95% CI [1.31, 11.74]), tobacco×cannabis×sex (β = -4.16, p = 0.03, 95% CI [-7.97, -0.36]), number of trials (β = -16.35, p = 0.04, 95% CI [-31.76, -0.94]), tobacco (β = 3.74, p = 0.04, 95% CI [0.19, 7.28]), tobacco×cannabis (β = -3.22, p = 0.11, 95% CI [-7.16, 0.73]), cannabis×sex (β = -1.48, p = 0.52, 95% CI [-6.00, 3.04]), sex (β = -0.86, p = 0.59, 95% CI [-4.00, 2.28]), tobacco×sex (β = 0.56, p = 0.73, 95% CI [-2.66, 3.78]). Post-hoc analysis of this three-way interaction tobacco×cannabis×sex revealed that only for males, the interaction between tobacco and cannabis was significant (β = -5.41, p = 0.03, 95% CI [-10.38, -0.45]). Furthermore, it was found that, only for male non-cannabis users, tobacco use was positively associated with SSRT (β = 8.76, t = 2.78, p = 0.005).

S7: List of studies provided raw data but were not included (plus reasons)

Baldacchino, A., Balfour, D. J. K., & Matthews, K. (2015). Impulsivity and opioid drugs: differential effects of heroin, methadone and prescribed analgesic medication. *Psychological medicine*, *45*(6), 1167-1179. *(Affective GNG was used)*

Behan, B., Connolly, C. G., Datwani, S., Doucet, M., Ivanovic, J., Morioka, R., ... & Garavan, H. (2014). Response inhibition and elevated parietal-cerebellar correlations in chronic adolescent cannabis users. *Neuropharmacology*, *84*, 131-137. *(Monthly alcohol use in grams unavailable)*

Berkman, E. T., Falk, E. B., & Lieberman, M. D. (2011). In the trenches of real-world self-control: neural correlates of breaking the link between craving and smoking. *Psychological science*, *22*(4), 498-506. *(Monthly alcohol use in grams unavailable)*

Choi, J. S., Park, S. M., Roh, M. S., Lee, J. Y., Park, C. B., Hwang, J. Y., ... & Jung, H. Y. (2014). Dysfunctional inhibitory control and impulsivity in Internet addiction. *Psychiatry research*, *215*(2), 424-428. *(No alcohol and tobacco use information)*

Christiansen, P., Cole, J. C., Goudie, A. J., & Field, M. (2012). Components of behavioural impulsivity and automatic cue approach predict unique variance in hazardous drinking. *Psychopharmacology*, *219*(2), 501-510. *(No tobacco use information)*

Colder, C. R., & O'connor, R. (2002). Attention bias and disinhibited behavior as predictors of alcohol use and enhancement reasons for drinking. *Psychology of Addictive Behaviors*, *16*(4), 325. *(Participants were too young (13-14 years old))*

Colzato, L. S., Ruiz, M., van den Wildenberg, W. P., Bajo, M. T., & Hommel, B. (2011). Long-term effects of chronic khat use: impaired inhibitory control. *Frontiers in psychology*, *1*, 219. *(No tobacco use information)*

Czapla, M., Simon, J. J., Friederich, H. C., Herpertz, S. C., Zimmermann, P., & Loeber, S. (2015). Is binge drinking in young adults associated with an alcohol-specific impairment of response inhibition? *European addiction research*, *21*(2), 105-113. *(No tobacco use information)*

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S8: Results on go RT in GNG task and SST

GNG

None of the substance-related variables had a significant effect on go RT. Age had a significant effect on go RT (β = 10.01, p < 0.01 , 95% CI [4.45, 15.58]), indicating a longer go RT when age increased. Working memory load had a significant effect on go RT (β = 91.71, p < 0.01, 95% CI [26.03, 157.39]), indicating a longer RT when there is working memory load. Percentage of no-go trials also had a significant effect on go RT (β = 115.94, p < 0.01 , 95% CI [57.15, 174.73]). This indicated that, when the stopping probability is low, there is strong readiness to give a response.

SST

The interaction of cocaine and tobacco smoking significantly predicted go RT (β = -8.19, p = 0.04, 95% CI [-16.05, -0.32]). Neither tobacco (β = -1.77, p = 0.68, 95% CI [-10.11, 6.58]) nor cocaine (β = -1.27, p = 0.82, 95% CI [-12.44, 9.90]) use alone significantly predicted go RT. Post-hoc analyses by splitting the imputed data sets and fitted the same restricted model without the interaction term revealed that for cocaine users, go RT non-significantly decreased as a function of tobacco consumed per day (β = -3.10, t = -0.38, p = 0.71), with an opposite non-significant pattern observed for cocaine non-users (β =4.30 , t = 1.03, p = 0.30). Age (β = 31.44, p < 0.01, 95% CI [22.82, 40.06]) and education years (β = -

13.47, $p < 0.01$, 95% CI [-21.06, -5.88]) had a significant effect on go RT. This indicated that go RT was longer as age increased, and was shorter as education years increased.

S9: Effect size comparison between studies included and those not included (plus **Fig. S4**)

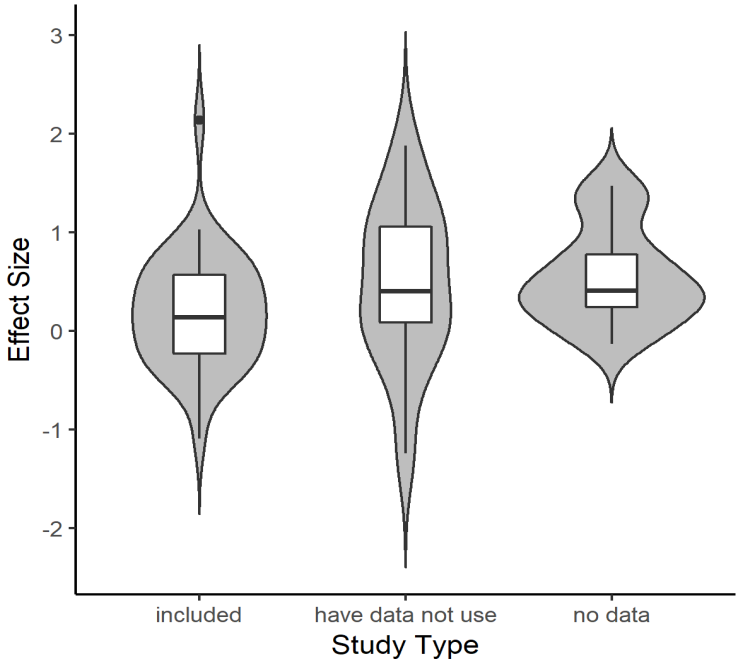
We calculated and compared the effect sizes of studies included, studies provided data but were not included, and studies that did not provide raw data.

Three online calculators were used:

1) http://www.polyu.edu.hk/mm/effectsizefaqs/calculator/calculator.html (mainly);
2) http://www.campbellcollaboration.org/escalc/html/EffectSizeCalculator-SMD28.php (only use for more than two groups *F* test, with each groups mean and N);
3) https://www.psychometrica.de/effect_size.html#fvalue (use point 6: ANOVA if only F value and sample size for each group are known; point 13: transformation into Cohen's d)

The one-way ANOVA indicated that there was no significant difference of effect sizes between the three kinds of studies (F (2,69) = 2.60, p = 0.08, **Fig. S4**).

Figure S4 Violin plot: effect size distribution compared between three study types



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